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Program Description

Overview

PTCOG58 celebrated the centenary of Ernest Rutherford's publication of the scientific paper confirming the discovery of the proton. The theme of the 2019 conference was **innovation** – scientific, clinical, technical and industrial – and how the worldwide growth of particle therapy will develop in years to come.
Objectives for the 58th annual conference were to:

- Address individual needs in compliance with their Continuous Professional Development (CPD) plan.
- Discuss the latest technological and clinical innovations in particle therapy.
- Identify educational resources, networks and other for exchange of knowledge and learning about particle therapy,
- Enhance the dialogue on clinical oncology across the NHS.
- Discuss the current research projects within the Particle Therapy Co-Operative Group (PTCOG) and enhance opportunities for future collaboration between groups of young researchers.
- Discuss the latest developments about practical clinical application of particle therapy.
- Describe diagnostics and treatments in the field of particle radiation therapy.

Target Audience

Healthcare professionals who treat cancer patients using radiation therapy/particle therapy and specifically:

- Radiation Oncologists
- Medical Physicists
- Dosimetrists
- Residents
- Radiation Therapists

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Poster Abstracts
Clinics: CNS
PTC58-0290

Hippocampal Sparing Radiotherapy in adults with Primary Brain Tumors: A comparative planning and dosimetric study using IMPT, IMRT and 3DCRT

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Introduction: We assessed the feasibility of hippocampal sparing in adults with primary brain tumors using Intensity Modulated Proton Therapy (IMPT) and compared this with Intensity Modulated Radiotherapy (IMRT) and 3D-Conformal Radiotherapy (3DCRT).

Methods and Materials: Twenty (20) patients were identified, and each patient underwent a radiotherapy planning CT scan and 2 MRI scans. A pre-operative diagnostic MRI scan was fused with the planning CT and used for target delineation and a dedicated 3T MRI scan at the time of planning was fused with the CT for hippocampus delineation. Three hippocampal sparing plans were generated for each patient with specific prescriptions (54Gy/30 fractions, 60Gy/30 fractions and 59.4Gy/33 fractions) using IMPT, IMRT and 3DCRT. Hippocampal sparing was defined as median dose to contralateral hippocampus $\leq$25Gy without compromising target coverage and organ at risk dose constraints.

Results: Hippocampal sparing was achieved in 19 patients (95%) with IMPT, 16 patients (80%) with IMRT and 13 patients (65%) with 3DCRT. The largest median hippocampal dose reduction was seen with IMPT, with a mean median hippocampal dose of 4.8Gy (range:0.0Gy-24.9Gy), 14.6Gy (range:1.9Gy-21.7Gy), and 16.2Gy (range:2.3Gy-25.0Gy) for IMPT, IMRT and 3DCRT respectively. Hippocampal sparing IMPT failed in one case with the largest tumor volume (650cc) where 2/3 of the hippocampus overlapped the target volume.

Conclusion: IMPT as compared to IMRT and 3DCRT plans showed a trend towards significant and effective hippocampal sparing in adult patients with primary brain tumors. We are currently evaluating this in a larger patient cohort and comparing IMPT with VMAT.

PTC58-0302

Radiation to the olfactory structure (OS) correlates with taste/odor changes during pencil beam scanning (PBS) proton irradiation for brain tumors

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Purpose: Patients undergoing brain irradiation report unpleasant taste/odor changes. Leveraging the capacity of PBS to define anatomic dose delivery by treatment layer in a time-dependent manner, this study sought to correlate timing of taste/odor changes with layer-defined dose delivered to the OS and Bragg peak location relative to the OS.

Methods: Patients receiving PBS craniospinal irradiation were enrolled on a prospective trial. Over three consecutive days, patients depressed a buzzer when taste/odor was detected and again when taste/odor dissipated. Each layer was assessed for number of days overlapping the taste/odor period, which was correlated with layer-defined OS dose and Bragg peak location relative to the OS.

Results: Of 10 patients enrolled, all experienced odor changes, and 3 noted taste changes. When the taste/odor period overlapped a treatment layer for 0, 1, 2 and 3 days, mean OS dose was 0.4, 2.7, 4.9, and 16.5cGyRBE, respectively. Fit to a normal-tissue complication probability model yielded TD50 of 4cGyRBE. Number of days that layers overlapped the taste/odor period correlated with location of the OS proximal to the Bragg peak ($p=0.036$). The OS was located proximal to the Bragg peak on 95% of layers overlapping the taste/odor period for all 3 days and on 3% of layers that never overlapped the taste/odor period.

Conclusion: Timing of taste/odor changes during brain irradiation correlates with layer-defined dose delivered to the OS and location of the OS proximal to the Bragg peak. Radiation-induced chemosensory changes in the OS may contribute to taste/odor changes patients experience during irradiation.

PTC58-0535

Unexpected severe optic pathway toxicity in a patient with meningioma treated with pencil-beam scanning proton therapy: A case report

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We report on a case of a patient treated with pencil-beam-scanning proton therapy (PBS-PT) who developed severe optic pathway toxicity despite all optical structures dose constraints being within well-established limits.

The otherwise healthy 50-year-old woman was treated with definitive PBS-PT for a skull-base meningioma with no ophthalmologic impairment at treatment initiation. The treatment was delivered in a single plan using three (two quasi-lateral and a vertex) fields up to 50.4 Gy(RBE) at 1.8Gy(RBE)/fraction. Nominal doses to optical structures were below 51Gy(RBE) (D2%).

Five months after treatment, the patient presented with visual field defect on the right eye, quickly deteriorating to amaurosis, followed shortly afterwards by visual field defect on the left eye. A diagnosis of radiation-induced optic neuropathy was confirmed on MRI, which showed inflammatory changes in both chiasmatic and proximal optic nerve regions.

Consequently, a comprehensive treatment review was performed, including nominal and log-file reconstructed dose distributions, delivery accuracy, plan robustness and LET distribution. As with the nominal dose distributions, log-file reconstructed doses resulted in low-risk dose levels in the optic structures (Table 1), and MR changes were in low LET (<3KeV/μm) areas (Fig.1). Robustness analysis, including fractionation, resulted in Max/D2 doses below 54Gy(RBE) for all optical structures (Table1).

After this comprehensive review, the observed toxicity could not be correlated to any dosimetric, delivery or LET based metrics. This may demonstrate that risk of toxicity is a complex, multi-variate problem also involving patient specific factors, and not just the oft-discussed issues of end of range LET/RBE and robustness.

PTC58-0157

Does alternating wide-angle arrangement of proton therapy to skull base lesion reduce the dose to temporal lobe?

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Bilateral opposite direction is a common treatment beam arrangement for proton therapy to a skull base lesion. It could avoid direct shooting to the brain stem and keep distal uncertainty far away from the most critical organ, which is the brain stem. However, the radiation doses in the proximal part of the proton beam are still high that makes a certain dose to bilateral temporal lobe when lateral opposite irradiation applying. Temporal lobe radiation injury may cause memory and cognitive function impairment that affect the quality of life. In this study, we evaluated the alternating wide-angle arrangement proton beams to skull base lesion in phantom to evaluate the effectiveness to sparing temporal lobe comparing to bilateral opposite direction. The alternating wide-angle proton beam angles were paired as 240-90 degrees and 120-270 degrees for treatment each day. One day treated with 240-90 degrees beams and 120-270 degrees on the other for the treatment course as following figure.

With the prescribed dose of 69.96Gy/33 Fractions to skull base lesion after optimization, the results showed that the mean doses of right temporal lobe were 41.78Gy and 39.40Gy for alternating wide-angle and bilateral opposite beam arrangements. The mean doses of left temporal lobe were 20.56Gy and 12.60Gy for alternating wide-angle and bilateral opposite beam arrangements.

Although the iso-dose coverage area of temporal lobe seems to less by alternating wide-angle proton beam arrangement in visual intuition, the alternating wide-angle proton plan did not demonstrate a numerical benefit for temporal lobe in dose volume histogram evaluation in this study.

PTC58-0328

The feasibility study of intensity-modulated proton therapy without range shifter for shallow brain tumors

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Purpose: Range shifter (RS) was widely used to treat superficial tumors in proton therapy. However, the commissioning of RS requires extensive measurements and the clinical usage of RS will take extra time to set up. We aimed to explore the feasibility of intensity-modulated proton therapy (IMPT) without RS for shallow brain tumors.

Methods and Materials: The study was approved by the local ethics committee. Ten patients with brain tumors were retrospectively selected. Two IMPT plans were created for each patient: same beam angles and beam number with and without RS. Both plans were generated by delivering prescription dose (60Gy[RBE]) to clinical target volumes (CTV). 2 or 3 beam angles were selected by experienced professionals and the same beam angles were used for both plans. All the plans were normalized to have CTV $D_{95\%}$ to the prescription dose. The dose-volume-histograms (DVH) indices for both CTV and organs at risk (OAR) were calculated to evaluate the plan quality and compared using the Wilcoxon rank sum test.

Results: Compared with the plans using RS, IMPT treatment plans using 2$\sim$3 beams without RS achieved comparable target dose homogeneity and hot spots, brain D_{max} and D_{mean}, brainstem D_{max}, spinal cord D_{max}, hippocampus D_{max}, optical nerve D_{max}, optical chiasm D_{max}, and pituitary D_{max} if at least one beam is able to cover the shallow region of the target.

Conclusions: Given appropriate beam angles and beam numbers, IMPT treatment without range shifter for shallow brain tumors is feasible.

PTC58-0717

Protonchorde: Improvement of local control in chordomas treated by proton therapy targeting hypoxic cells revealed by 18F- FAZA PET/CT tracers: preliminary results

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Purpose: To increase the total dose of 10% at the level of hypoxic cells only a dose of 78 GyRBE (against 70 Gy in the rest of the lesion) to improve local control at 3 years of 15% or from 71% to 86%.

Partial Results: All patients showed good tolerability. The median follow-up was 12 months (range: 3 –24). No local or distal relapse has been detected. Two patients died (#3 by pulmonary embolism and #5 by acute pancreatitis). All other patients are alive

Conclusions: Our preliminary results are very encouraging in terms of good tolerance of treatment at high doses and this thanks to metabolic imaging that allows us to study tumor heterogeneity and target the most radioresistant hypoxic cells.

PTC58-0690

Criteria for selecting patients with grade 2-3 brain tumors to proton therapy

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Background: Region Skåne, Sweden and The Capital Region, Denmark have a collaboration concerning proton therapy (PT) at The Skandion Clinic, Uppsala. We estimated the utilization PT as a replacement to image-guided volumetric modulated arc photon radiation therapy (IG-VMAT), for low-grade brain tumors based on common criteria.

Methods: We retrospectively reviewed our records and the selection of PT patients during 2015-2018. We evaluated the dosimetric benefit for eyes, lacrimal glands, pituitary gland, hippocampi, and uninvolved brain dose was examined as part of the decision-making. The comparison of clinical alternative plans with realistic treatment planning margins based on the positioning uncertainty of the respective modalities, i.e. IG-VMAT or PT.

Results: During the period, 43 patients with intra-cranial disease were treated with PT. Children and patients with PS >2 were excluded. Selected patients for PT was brain tumors grade II-III, primarily astrocytomas and oligodengrogliomas with favorable prognostic factors. The patients had 1-6 evaluated organs at risk with lower average dose of about 5 Gy with PT, typically with a considerable reduction of the 10-30 Gy volumes. The median average dose to the brain was 4.9 Gy lower with PT compared to IG-VMAT. About forty percent of the evaluated patients were sent to PT.

Conclusions: About 40% of the evaluated patients were treated with PT. The dosimetric benefit depended on tumor location, which may translate to clinical outcomes advantage though this is at the present not clarified.

Clinics: Base of Skull

PTC58-0382

Neutron radiotherapy followed by a proton boost for locally advanced salivary gland tumors: Early clinical experience

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Purpose: Despite improvements in local control with neutron therapy in salivary gland tumors, caution is required near vital CNS structures. A mixed neutron and proton boost approach can potentially maximize local control while minimizing toxicity. We report our early clinical experience.

Materials and Methods: From 2014 to 2018 we retrospectively reviewed 29 patients with locally advanced salivary gland tumors. Median age was 56 years, patients had ACC histology (79%), T4 disease (86%) skull base invasion (86%) and orbital invasion (31%). Five patients had prior radiation. Fifteen patients (51.7%) had pre-RT resection of which only 2 were GTR with negative margins. Median neutron dose was 18.4 Gray (Gy). Proton boost dose ranged from 16 to 45 Gy (RBE). Toxicity was graded as per CTCAE v4.03.

Results: At a median follow up of 15.4 months (IQR, 5.8-24.1), locoregional recurrence occurred in 4 patients, distant recurrence in 2 patients and death in 2 patients. The 2-year actuarial locoregional control, progression free survival and overall survival were 93.1%, 89.7% and 96.6% respectively. Excluding re-irradiated patients, common recorded acute grade 3 toxicities were mucositis (50%) and dermatitis (37.5%). There were no documented acute grade 4 or 5 toxicities. Late Grade 3/4 late include trismus (4%), hearing loss (8.3%) and expected visual loss (25%). Radiation necrosis of the bone occurred in 2 patients and the brain in 2 patients.

Conclusion: In this challenging cohort of patients, early outcomes for this novel approach are promising and compares favorably with our historical experience with NRT alone.

PTC58-0730

Proton therapy versus volumetric modulated arc therapy for benign tumors of the skull base and sellar location

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Background: The skull base and sella are surrounded by critical neural organs at risk and thus minimizing the integral dose while treating tumors in this location is advantageous. Our aim is to evaluate the dosimetric differences of volumetric modulated arc therapy (VMAT) as compared to 3-D proton therapy (PBT).

Methods: Ten patients with pituitary adenomas (N=5) and skull base meningiomas (N=5) who were treated with PBT and had a comparison VMAT plan available were evaluated. The average mean and maximum doses to the bilateral optic structures, cochlea, and nearby brain were compared across treatment modalities using a paired Student's T-test, with use of the Bonferroni correction for multiple comparisons.

Results: Median dose was 50.4 CGE (45-52.2). Target volume coverage was comparable in both proton and VMAT plans for all cases. Compared to VMAT, PBT plans showed a significant reduction in mean and maximum doses to the right lens and eye, with a trend towards a significant reduction for the mean dose to the right optic nerve. Doses to other structures were comparable between plans, with a trend towards lower doses for proton plans.

Conclusions: PBT as compared to VMAT resulted in meaningful dose reductions to organs at risk while maintaining comparable target coverage. Further refinements in proton therapy including intensity modulation may have the potential to further minimize dose to critical neural structures in the skull base and sellar location.

PTC58-0613

Use of optical coherence tomography (OCT) as routine base line examination in meningioma patients before proton beam radiation

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Introduction: The assessment of visual field (VF) measured via automatic perimetry (AP) is a standard examination. Optical coherence tomography (OCT) is a non-invasive, non-contact and painless imaging technique that provides high-resolution measurements and cross-sectional imaging of the retina and retinal nerve fibre layer (RNFL). The RNFL thickness is of particular interest in clinically manifest as well as subclinical optic neuropathies.

Methods: Visual parameters including VF and RNFL thickness were measured before start of radiation. VF was measured by AP, RNFL via OCT. The examination was performed prior to treatment planning for proton therapy. Additionally, the involvement of the anterior visual pathway (optic nerve, chiasma) was defined on the planning MRI.

Results: Twenty-four patients with no ophthalmologic comorbidities were included. The mean age at time of radiation was 55.4 a (+/- 12.8 a). At baseline a restriction of the VF was detected via AP in 12 patients on the left and in 7 patients on the right. Via OCT in 13 patients a deficiency was detected on the right side and in 9 patients on the left. On MRI the right optic nerve was in direct contact to the meningioma in 13 patients, the left optic nerve in 16 and the chiasma in 11 patients, respectively.

Discussion: In this cohort the detection of the anterior visual pathway disorders was higher with OCT compared to AP. OCT provides additional base line information which is beneficial for treatment planning, follow-up and as endpoint in future clinical trials.

PTC58-0572

A new combined proton-photon strategy for dose escalation in clivus chordoma irradiation

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This work describes new irradiation strategies to reach therapeutic dose (72-74GyE) in clivus chordoma - a challenge because of OAR proximity that often leads to tumor undercoverage.

For 10 patients, sequential boost plans were computed with proton SFUD and IMPT with 50.4 GyE (1.8GyE/fraction) delivered to the Low Risk CTV (LRCTV) and 23.4 GyE to the High Risk CTV (HRCTV). Simulated Integrated Boost (SIB) plans were also computed with both SFUD and IMPT to deliver 73.5 GyE (2.1 GyE/fraction) to the HRCTV, the LRCTV receiving 56 GyE (1.6 GyE/fraction). A new combined proton-photon strategy consists in irradiating LRCTV with proton SFUD or IMPT (50.4 Gy) with Stereotactic Body Radiotherapy (SBRT) to add 22 Gy RBE (2GyE/fraction) to the HRCTV.

Proton plans were computed with RayStation 6.0 (RaySearch Laboratories, Sweden) with a CTV-based robust optimization (3% of the range for range uncertainties and 3mm for metric uncertainties). SBRT treatments were planned with Cyberknife® on Multiplan 5.3 (Accuray, USA).

OAR dose constraints were evaluated following the ICRU91 and ICRU78 recommendations for SBRT and protons plans respectively. All plans are clinically deliverable and respect the OAR constraints – differences between the plans are about tumor coverage, conformality and homogeneity. Figure 1 shows clearly that in average, IMPT-SIB achieved the best tumor coverage for LRCTV and HRCTV for protons-only plans. However, the best tumor coverage for both volumes was reached for the combined proton-photon technique including SBRT. An example of isodosis obtained for 3 different techniques is shown for one patient in Figure 2.

Clinics: Eye

PTC58-0684

Outcome and visual prognosis on a series of patients, stage T1 post choroidal melanoma treated with proton therapy at ICPO

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Method: Between 11/91 to 12/10, 8399 patients treated for a choroidal melanoma were recorded in the Institut Curie database. Among them, all patients with stage T1 choroidal melanoma treated with proton irradiation and with a minimal follow up of 5 years, were selected. They were divided in two groups depending on the distance between Tumor and Macula or Papilla (T-M/P). Group 1: T-M/P $>$ 3 mm and Group 2: T-M/P $<$ 3 mm. Survival and functional impact on vision were analyzed.

Results: Four hundred twenty-four patients were selected. The Gender Ratio (F/M) was 51.9%/48,1%, The mean age was 56,2 Years (5,1– 23). The median follow up: was 10,5yrs ((5,1 – 23). Local recurrence rate was 0%. Overall survival rate was 91,7 % at 10 yrs IC $_{95\%}$ [88,6% - 94,9%]. Initial Visual acuity (VA): Group 1 $>$ Group 2. At last f-up, VA: Group 1 $>$ Groupe 2 (p=0,03). Impact of proton therapy on VA score was related to the distance between tumor border and macula or papilla limits. At last follow up 70% of pts from Group1 had VA $\geq$ 20/40 and 50% of pts from Group2 had a VA $>$ 20/200.

Conclusion: This analysis of a series on selected patients with T1 posterior choroidal melanoma with a long follow up shows excellent local and overall survival rates, and significant visual function conservation depending on the distance between the tumor and the macula / papilla.

PTC58-0326

Preclinical commissioning of a new eye tracker device in CNAO

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An Eye Tracking System (ETS) is used at CNAO for providing a stable and reproducible optical proton therapy (OPT) setup, featuring a fixation light (FL) and monitoring stereo-cameras embedded in a rigid case. The ETS is mounted on industrial robots to accurately position the FL according to patient-specific gaze direction (polar/azimuth) established during treatment planning (Eclipse, Varian).

An upgraded ETS is proposed for an improved clinical workflow standardization and simplification. We discuss these hardware and software updated and their pre-clinical commissioning.

The revised ETS design operates with the main systems already in use at CNAO featuring reduced dimension since part of the electronics is moved out of the device (Figure 1, panel a). The use of a single cable and standard connectors for signals improved the device connectivity. The visibility of the FL is improved due to tunable LED intensity.

An ETS setup simulator algorithm is developed to automatically provide the FL positioning in space avoiding interferences with patient, beam and other hardware (Figure 1, panel b). Algorithm validation was performed simulating ETS setup of 30 patients already treated at CNAO.

Differences between the position of ETS reference points estimated by the algorithm and those measured by the in-room imaging system are presented in Fugure2. The corresponding deviation of the gaze direction is on average 0.17°polar and 0.60°azimuth.

A more reliable hardware-software package for OPT has been presented ensuring ETS positioning with an average accuracy of 1.5 mm corresponding to deviation of gaze direction lower than 1°.

PTC58-0714

Commissioning of eye treatment with rotating gantry and energy scanning carbon-ion beam

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At the Heavy Ion Medical Accelerator in Chiba (HIMAC), more than 200 ocular melanoma patients have been successfully treated by carbon-ion beams since 2001. Traditionally, the vertical and horizontal port with the passive beam delivery system were used to irradiate target volume. To evaluate the advantage of use of rotating gantry and energy scanning carbon-ion beams for choroidal malignant melanoma, we have started the commissioning of the treatment from 2017. The treatment techniques are mostly the same as generally used in HIMAC except for the suturing titanium clips to the outer sclera surface for target positioning. To make the effective dose calculation possible using treatment planning system (TPS), computed tomography (CT)-based treatment planning is employed. By evaluation of the dose distribution, energy scanning with rotating gantry showed to be equal to superior compared to traditional passive scattering method. An evaluation of dose calculation and beam delivery accuracy has proven that the ocular melanoma treatment with rotating gantry and energy scanning carbon-ion beam was feasible.

PTC58-0520

A prospective international Survey on Ophthalmic Radiation Therapy Toxicity (SORTT)

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Purpose: Radiation plays an important role in the treatment of ophthalmic malignancies. Though many different radiation modalities (i.e. protons and brachytherapy) can be used to destroy ocular tumors, each varies in the irradiated volume. Therefore, we can expect a difference in the incidence and location of side effects as well as in functional outcomes. However, there are only strikingly few comparative studies or staging systems available to collect the incidence and impact of ophthalmic radiation.

Methods: After plenary meetings during the Eye Cancer Working Days in Paris and Sydney, a prospective international survey was started. Ophthalmic and radiation related data fields were fashioned collecting both treatment and outcomes. Patient privacy and ethics protections were incorporated into an internet-based registry to prospectively track outcomes for patients after ophthalmic radiation therapy. These include brachytherapy as well as external beam radiotherapy with protons and photons. After an initial year-long enrollment period, patients will be followed for at least 3 additional years.

Results: Twenty-one centers from 6 continents agreed to join this prospective registry. They are currently obtaining local IRB and ethics approvals. Patient accrual has been launched on January 1, 2019.

Conclusions: This database will support the creation of a dedicated ophthalmic radiation side effects grading system, and accumulate evidence about risks associated with currently used ophthalmic radiation modalities. Such data may lead to preferred radiation practice patterns and staging systems in treatment of ocular tumors. We hope this study will lead to improved local control and less toxicity among ocular tumor patients.

PTC58-0099

Surgery and proton therapy of conjunctival melanomas

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Introduction: Conservative strategies of conjunctival melanomas include no touch surgery and adjuvant treatments including cryotherapy, mitomycin and radiation therapy. Outcomes after postoperative proton therapy are reported.

Material and Methods: Monocentric retrospective study of consecutive patients treated between 1992 and 2018.

Results: Characteristics of 92 patients were age 63yo, male 55%, *de novo* 21%, nevus 14%, melanosis 65%, T1 71%, T2 15%, T3 14%, unifocal 83%, peribulbar 85%, > 90 degrees 69%, epithelioid 40%, thickness 2.5mm [1.0-4.0], diameter 7.0mm [4.5-10.0], incomplete resection 58%, ulceration 15%. Median follow-up was 2.7 years. Five-year local failure rate was 33%. Of 25 local recurrences, 52% were marginal/out-of-field, 20% in-field, 28% unspecified. First surgery at expert center resulted in 19% (vs not: 34%) local relapses, p=0.16, with salvage exenteration in 14 patients. Tumor stage, angular involvement were significant factors for local relapse. Five-year progression-free survival and cause-specific death rates were 62% and 4%. Clinical stage and epithelioid type were prognostic factors for poorer progression-free survival. Grade 3 trophic toxicity occurred in 22.9% of patients and was treated locally, with grafts in 14% of cases. Hypertonia occurred in 14%, cataract in 22. Visual acuity, assessed in 61 patients, was stable/improved in 57%. Prognostic factors for visual deterioration were age, tumor extent (multifocality, angular involvement > 180 degrees) and cryotherapy.

Conclusions: 5y local failure rate after postoperative proton therapy was 33% with most failures being out-of-field and resulted 15% non-conservative salvage treatments. Mitomycin was not associated with improved local control. Toxicities were overall manageable.

PTC58-0536

Use of a compensator in proton therapy for large conjunctival melanomas

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Introduction: Adding a compensator to the postoperative proton therapy of conjunctival melanomas can reduce irradiated ocular volumes and may reduce toxicities in case of large surface tumors. With the use of mitomycin, smaller prophylactic volumes are irradiated. However, most local failures occur out-of-field (see clinical abstract). We assessed toxicities depending on the use of a compensator.

Materials and Methods: In this retrospective study, consecutive conjunctival melanomas patients were treated from 1992-2017. The use of a compensator was associated with tissue gel equivalent bolus. Lid retraction was performed if conjunctival fold were not involved, involvement requiring the use of a compensator.

Results: Of 66 patients, age 63, over 90° involvement N=44, PAM N=37, 40 had a compensator. Use of a compensator was highly correlated with large tumor surface (p<0.001) and inversely corelated with mitomycin (p=0.002). Larger volumes of surface structures (corneal/conjunctiva/eyeball) were irradiated with the use of a compensator, again corelated with tumor surface, suggesting that tumor coverage was maintained for large surface tumors. Surface structure complications were borderline significantly with the use of a compensator (53 vs 93%,p=0.065). The lens was significantly less irradiated with a compensator (p<0.001).

Conclusion: With the use of a compensator, which is highly correlates with large tumor surface, toxicities were manageable. Data on lid toxicity will be presented at PTCOG2019. Propensity score matching on the surface involved and local control will be assessed to account for a possible increase in EBR using a compensator (resulting in end of SOBP at the ocular surface)

Clinics: Pediatrics
PTC58-0504

The impact of a proton therapy facility on radiotherapy practice patterns at a children's hospital

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Introduction: In October 2016, Cincinnati Children's Hospital (CCHMC) opened a proton therapy center. We report the impact of this center on the volume and type of radiotherapy delivered for patients served by CCHMC.

Methods and Materials: Records for CCHMC patients treated in the 12 months prior to, and 24 months following the opening of the proton center were analyzed for distribution of diagnoses, treatment modality, treatment intent and referral source.

Results: In the 12 months prior to opening the proton center, 93 unique patients received 103 courses of photons. In the 12 months following opening of the center, 142 patients received 151 courses of radiotherapy – 52% with protons. In the second 12 months following opening, 160 patients received 180 courses of radiotherapy – 56% with protons. Prior to protons, 72% of treatment courses were considered definitive, with 86% categorized as definitive after protons were introduced. Most patients with solid tumors are now treated with protons (Figure 1). Prior to the proton center, 5 patients (5%) were directly referred from outside institutions. In the one- and two-year periods following protons, 36 (25%) and 40 (25%) patients were direct outside referrals for radiotherapy – most often for sarcomas or CNS tumors (Figure 2).

Conclusions: Opening a proton center at a children's hospital had a significant impact on the number of patients and diagnoses treated with radiotherapy. These data can inform new centers in resource allocation needed for potential changes in patient population.

PTC58-0560

Particle versus photon radiotherapy impact on toxicity in children: Which evidences?

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Objective: Evaluating the place of particle therapy (PT), from a literature review on toxicity.

Methods: Publications dating from 1997-2017 (pub) were retrieved from Medline. Dosimetric investigations (group 1), secondary cancers predictive models (K2: group 2), and clinical series (group 3) were evaluated and focused on inter-comparisons between PT and XR (3D/IMXRT photons), on 16 toxicity items, along with significance (*pS* if $>$.05).

Results: One hundred sixty-three (163) articles were selected, with 145 evaluable (54 pre-clinical and 91 clinical) including 40 (27 pre-clinical and 13 clinical) inter-comparing PT and XR for toxicity (as single or multiple events):

- Group 1 pub (349 analyzed children): 14 CNS, 3 head and neck (HN), 3 thorax, 4 pelvis and abdomen
- Group 2 pub ($=$ 126 children): 15
- Group 3 pub ($=$ 1249 children): 4 CNS, 1 HN, 3 endocrine, 1 lung, and 3 acute tolerance

Discussion:

- Group 1: P$>$XR with *pS* in 8/10 brain, 6/10 cochlea, 4/8 endocrine, 2/3 visual, 2/3 bone, 4/4 heart, 3 /4 digestive tract (pancreas conflicting), 2/2 lung, 2/2 breast, 1/6 cognition+IQ. P$\leq$XR: 0.
- Group 2: P$>$XR with *pS*: 7/22. P$\leq$XR: 0.
- Group 3: P$>$XR with *pS*: 1/1 brain, 2/2 cognition+IQ (schooling contradictory), 2/3 endocrine, 2/3 acute. P$<$XR with *pS*: 1/1 lung, 1/1 salivary.

Conclusion: All groups 1+2 and most group 3 evidenced the superiority of PT, although *pS* value was not systematically quoted. No clinical intercomparison was randomized. If CNS seems well documented, schooling performances are still debatable and other sites are poorly documented, or controversial, such as lungs and pancreas.

PTC58-0249

The dosimetric significance of Pencil-Beam-Scanning-Proton-Beam-Therapy lateral penumbra on the vertebrae superior and inferior to the treatment field in paediatric radiotherapy

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Background: Partial irradiation of the vertebrae in children may lead to future growth asymmetry. Therefore, any adjacent vertebra unable to be adequately spared from radiation is usually included. This work evaluates the lateral penumbra of Pencil-Beam-Scanning-Proton-Beam-Therapy (PBS-PBT) compared with Intensity-Modulated-Arc-Therapy (IMAT) and its dosimetric impact on the vertebrae within and at the edge of the treatment field.

Methods: Twenty pediatric abdominal neuroblastoma cases were double-planned using PBS-PBT and IMAT to 21Gy in 14 fractions, optimized to produce a rapid dose fall-off at the superior and inferior vertebrae. All PBS-PBT plans required a 5cm range-shifter. The lateral penumbra was measured as the 20%-80% isodose distance in the cranio-caudal direction along the anterior vertebral body. Dose to the superior/inferior (n=39) and adjacent (n=20) vertebrae were analyzed.

Results: The lateral penumbra was larger with PBS-PBT than VMAT by 2.8mm (median 8.9mm vs. 6.1mm,p=0.0001). There was no statistically significant difference between both plans for superior/inferior vertebrae V20Gy,V10Gy,mean dose,D50% or D2%. There was marginally lower superior/inferior vertebra D95% coverage with PBS-PBT than VMAT (median 0.71Gy vs 1.79Gy,p=0.000). However, this was appropriately reflected in the reduced dose coverage to the adjacent vertebrae with PBS-PBT V20Gy (median 95.3% vs 99.7%,p=0.001) and D95% (median 20.1Gy vs. 20.6Gy,p=0.001).

Conclusion: These results suggest that the slight differences were likely due to inter-planner variability on the position chosen to optimise dose fall-off rather than an effect from increased PBS-PBT lateral penumbra. As these values were within accepted range clinically, we conclude that the increased PBS-PBT lateral penumbra has a minimal impact on vertebral dosimetry.

PTC58-0700

Monitoring and management of anatomical variations during proton therapy treatments in pediatric patients

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Introduction: Proton therapy (PT) is increasingly being used for pediatric tumors. This is mainly due to the advantages with respect to conventional therapy in terms of organs at risks (OAR) sparing. It is known that PT is more sensitive to anatomical/density modifications. Aim of this study is to present our experience in monitoring and managing anatomical variations in cranial and spinal pediatric lesions.

Materials and Methods: Five cases, with different histology and location, were studied:1 Skull base chordoma, 1 supratentorial glial neoplasm with hygroma, 1 craniopharyngioma with cystic component, 1 glial tumor of the posterior cranial fossa with vermian residue and 1 atypical meningioma with residual disease in close proximity with the cervical cord. Each patient underwent several CT and MR scans over the treatment course. The following MR sequences were acquired: T2 (study of the cystic and hygromatous component), 3D Flair (study of the edemigenous component), 3D T1 (OAR anatomical definition), DWI (study of cellularity).MR imaging was used to outline target and OAR on the control CTs, then the nominal plan was re-calculated on the CT. In case of target under dosage or OAR constraints violation a re-planning occurred in order to recover the initial dose prescription/constraints.

Results: A total of 9 CT and 15 MR were acquired in this study. Only in 1 case the re-planning was needed due to the increase of the cystic component in a craniopharyngioma.

Conclusions: Monitoring and management of anatomical variations via repeat imaging is feasible in pediatric patients and in some cases, it was used to trigger replanning.

PTC58-0313

Utilising national data in health service research for proton therapy: A paediatric example

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Purpose: Data plays a key role in service planning and health service research. Although there is a limited quantity of proton therapy (PBT) data available, there is a wealth of incidence and conventional radiotherapy (CRT) data. We investigate how Public Health England (PHE) pediatric incidence and CRT can be used to inform the national proton therapy (PBT) service by looking at variations across England.

Methods: PBT-relevant incidence data (patient, tumor, geographical event information) was obtained from PHE, excluding NHS Proton Overseas Programme (POP) activity. Paediatric incidences (age$<$16) were extracted. The data was geographically grouped by clinical network (CN). Age-standardised rates (ASR) for CNs were calculated as incidences per 100k under-16 population. Conventional RT utilization (CRTU) divides the number of incidences with an RT record by the total number of incidences. The results were used to create heat-maps for England.

Results: Figure 1 displays the CN heat-map for ASR and Figure 2 the CRTU heat-map. There are clear variations in incidence rates between CNs. Wessex has the highest ASR (20.5 incidence per 100k) and East-Midlands the lowest (16.7 incidence per 100k). There is also variation in CRTU across England. Thames valley has the lowest CRTU in pediatric incidences of relevance to PBT, with only 20% receiving CRT, while Northern England has the highest with 37.7%.

Conclusions: National cancer data has increased in quality and granular data can assist in PBT health service research. This data can estimate additional referral numbers or potential current under-referral numbers and ensure equity of access.

PTC58-0644

Proton beam therapy in pediatric patients with brain tumors

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Purpose/Objective: We report a collaboration experience between two institutions and clinical outcomes in proton-beam-therapy (PBT) of pediatric brain tumors.

Material and Methods: From November 2015 to January 2019, 13 consecutive patients (Male/Female: 9/4; median age 5 years [range 1-17]) with brain tumors were treated with PBT. Five patients had Medulloblastoma (one standard risk), 2 Pylocitic Astrocytoma, 1 Pituitary Germinoma, 1 parietal Choroid Plexus carcinoma, 1 grade II Meningioma of the interpeduncolar cistern contiguous at III cranic nerve, 1 Pituitary retrochiasmatic Craniopharyngioma, 2 Atypical theratoid rhabdoid tumors. Eleven patients underwent surgery before PBT (partial resection: 6, subtotal resection: 4, gross total resection: 1). Various chemotherapy regimens were received by 11 patients following specific clinical protocol. Toxicity was scored using the Common Terminology Criteria for Adverse Events Version 4.0. Median total delivered PBT dose was 54 Gy RBE in 1.8 daily fractionation. Nine patients received daily anesthesia during radiotherapy course.

Results: The therapy was completed by all patients and was well tolerated without interruptions. With a median follow-up of 17 months [range: 8-38] all patients are alive. Twelve patients are in complete remission/stable disease, one in progression. Grade 3 acute toxicity of neutropenia and fatigue were experienced by 3 patients. Two patients experienced late toxicity: one had intracranial bleeding self-solved and one developed asymptomatic cavernoma.

Conclusion: Our experience has shown the good tolerability of PBT. Efforts to reduce complications are warranted. Further follow-up will allow to better evaluate long-term sequelae.

PTC58-0048

What is the clinical outcome of proton beam therapy for pediatric patients with medulloblastoma in Korea?

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Purpose: To evaluate clinical outcome of pediatric patients with medulloblastoma treated with proton beam therapy (PBT) at National Cancer Center (NCC), Korea.

Methods: Thirty-six pediatric medulloblastoma patients treated with PBT between July 2004 and December 2015 at NCC, Korea were retrospectively analyzed. Thirty-two patients treated with curative aim were included, and 4 re-irradiated cases were excluded. We calculated overall survival (OS) and progression-free survival (PFS) rate and reviewed treatment-related acute toxicities.

Results: The median follow-up duration was 49months (range, 7-113). The median age at PBT was 7(range, 2-20). Twenty-six patients were high-risk (HR) cases. Most (except 2) received craniospinal irradiation (CSI) with median CSI dose of 36.0Gy(range, 23.4-39.6) and median total dose of 55.8Gy(range, 32.4-61.2). The median interval from operation to PBT was 37days (range, 21-845). Ten patients showed disease relapse, among them 5 patients dead at the time of analysis. The 3-year OS and PFS for all were 87.3%, and 71.6%. The 3-year OS and PFS of HR were 84.3% and 65.0%; 88.2% and 65.8% for M+stage, 90.5% and 66.7% for residual-disease$>$1.5cm^3, and 71.4% and 57.1% for $\leq$3years, respectively. There was minimal treatment gap during PBT, the median PBT duration being 46days (range, 33-52). Concomitant chemotherapy was used in 14 patients in HR, and they showed higher acute toxicities compared to the patients without concomitant chemotherapy.

Conclusions: The patients referred to NCC, Korea for PBT were mostly HR patients. Although the treatment referral was mostly from outside the hospital, treatment interval and duration were kept optimal. The clinical outcome was reasonably good considering the advanced nature of disease.

Clinics: Breast
PTC58-0706

Cardiac and lung sparing in breast radiotherapy, proton and photon planning study with free (FB) and breath hold (BH) technique

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Purpose: Proton therapy of left sided breast cancer can be advantageous in comparison to photon treatment in terms of cardiac sparing. The choice of FB or BH technique depends on the anatomy of patient. Main goal of this study was to assess the benefit from using breath hold or proton therapy in early breast cancer adjuvant radiotherapy.

Materials and Methods: The data form six breast cancer patients were used to prepare treatment plans with photons and protons (on both: FB and BH). Photon plans included tangential fields, while proton plans contained fields from anterior-oblique direction. Prescribed dose for those plans was 50 Gy or 50 Gy(RBE) in 25 fractions. All plans fulfilled dose distribution criteria in the PTV and optimal sparing of the heart, left anterior descending artery (LAD) and lungs was attempted. Statistical tests were used for dosimetric comparison of all plans.

Results: We found that in proton plans mean dose to the heart, LAD and lung was significantly reduced, at least by a factor of 2. Results are presented in the table 1.

Conclusions: The proximity of the heart and LAD to the target makes the irradiation of the left-sided breast challenging. These results show that proton technique could lead to promising cardiac and lung sparing, especially when BH treatment with photons is not possible or in patients with significant cardiac comorbidities. We did not reveal further dose reduction in protons while using breath hold, as it is in the case of a photon technique.

PTC58-0316

Critical appraisal of the potential role of IMPT for advanced breast cancer

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Purpose: To investigate the role of intensity modulated proton therapy (IMPT) for advanced breast carcinoma in comparison with volumetric modulated arc therapy (VMAT).

Methods: A cohort of 20 patients (10 breast-conserving and 10 post-mastectomy patients, the latter with tissue expander implants) was retrospectively planned for locoregional treatment using VMAT and IMPT. Proton plans were computed with or without robust optimization methods. Plan quality was assessed by means of quantitative analysis of the dose volume histograms and scored with conventional metrics. In addition, estimates of the risk of secondary cancer induction (excess absolute risk, EAR) were performed according to a model inclusive of fractionation, repopulation and repair.

Results: Concerning target coverage, the data proved a substantial equivalence of VMAT and IMPT. Organs' at-risk planning aims were achieved for all structures for both techniques but IMPT plans presented the best results. Robust optimization impacted on the near-to-maximum dose values for contralateral lung and breast, on the mean dose for the heart and ipsilateral lung. The numerical values of EAR per 10′000 patients-year resulted about one order of magnitude higher for VMAT then for IMPT for contralateral structures (∼11-14 vs ∼0.9-1.4 for VMAT and IMPT respectively) and about a factor two for the ipsilateral lung (∼35 vs 19). The robust optimization methods induced a deterioration in the EAR estimates.

Conclusion: This study suggests that IMPT is a potentially promising approach for the radiation treatment of advanced breast cancer when nodal volumes should be irradiated. Clinical trials should be performed to demonstrate the anticipated dosimetric benefit.

PTC58-0142

Dosimetric comparison of proton versus photon therapy for bilateral breast/chest wall and comprehensive nodal irradiation for synchronous bilateral breast cancer

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Purpose: Adjuvant radiotherapy for synchronous bilateral breast cancer poses distinct treatment planning challenges. This study is a dosimetric comparison of proton beam therapy (PBT) versus photon therapy for bilateral breast/chest wall and comprehensive nodal irradiation (RNI) for synchronous bilateral breast cancer.

Methods: Patients with synchronous bilateral breast cancer treated with bilateral radiotherapy to the breast/chest wall and RNI at our institution between 2015 and 2018 were identified. Comparison plans were generated by an experienced dosimetrist and reviewed by a radiation oncologist.

Results: Nine patients were included in this analysis. Volumes included bilateral postmastectomy radiotherapy (n=7), bilateral whole breast radiotherapy with RNI (n=1), and postmastectomy and whole breast radiotherapy with RNI (n=1). CTV included breast/chest wall and regional lymph nodes, including axilla, supraclavicular fossa, and internal mammary chain. PTV was 5 mm expansion on CTV. Prescription to the CTV (PBT) or PTV (photon) was 50 Gy (or relative biological effectiveness 1.1) in 25 fractions. Five patients received boost to chest wall (n=2), lumpectomy cavity (n=1), and nodal regions (n=3). Boost was delivered as simultaneous integrated boost to 54.05-58.75 Gy in 25 fractions (n=5) or sequential boost of 12.5 Gy in 5 fractions (n=1). Table 1 lists dose received by 90% and 95% of volume (D90% and D95%, respectively). Table 2 lists dose to organs at risk.

Conclusion: Bilateral breast/chest wall and comprehensive nodal PBT for synchronous bilateral breast cancer is associated with improved target coverage and normal tissue sparing compared to photon therapy. PBT is an attractive treatment option for these complex patients.

PTC58-0729

Re-irradiation of recurrent cancer in the breast and chest wall using intensity modulated proton therapy

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Background: Treatment management is challenging in patients with local recurrence of breast cancer who had previous radiation therapy. This series described technique and outcome for 10 such patients treated at Scripps Proton Therapy Center.

Methods: Of 10 patients in this category, two patients needed chest wall radiation after resection of recurrent cancer due to positive margins; seven patients had gross nodal and chest wall recurrence; one patient had post-lumpectomy radiation in previously irradiated area from another malignancy. All patients except one (23.4 Gy) had previous full dose radiation to 50 Gy or higher. Patients, immobilized with either a breast board or Vac-Q-Fix cushion, were set up in the supine position with arms over their head. One to two beams using IMPT with MFO technique was used. Dose was prescribed at 1.8-2 Gy to 50 to 60 Gy daily treatment. Weekly adaptive simulation was done with CT. Photographs were obtained during and after treatment. All cases were reviewed and approved by our weekly physicist and physician treatment planning conference.

Results: No patients had more than grade 2 skin acute toxicity. There was no Grade 3 or greater late toxicity. One patient developed grade 2 lymphedema. Only one patient had local failure, and two died from distant metastases.

Conclusion: IMPT is feasible and a safe modality for re-treatment of recurrent cancer in the breast and chest wall. Further validation with more patients and longer follow-up is needed.

PTC58-0731

Accelerated partial breast irradiation (APBI) with intensity modulated proton therapy (IMPT) for patients with breast augmentation

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Background: Patients with early stage breast cancer and breast augmentation often require mastectomy or have significant cosmetic issues from whole breast irradiation. We describe technique and outcome in six patients treated at Scripps Proton Therapy Center.

Methods: All patients have either T1 No ductal (5) or uni-focal DCIS (1). All patients met ASTRO criteria for APBI. All patients underwent CT based simulation and treatment planning and were set up supine on a breast board or in the prone position. Daily setup and localization were accomplished with 3-4 skin surface fiducial markers tracked with orthogonal x-ray pairs. 40 Gy and 34 Gy in 10 treatments were prescribed lumpectomy cavity and lumpectomy cavity plus 1-1.5 cm excluding chest wall and skin. Treatment was delivered using IMPT with a single enface field with simultaneous integrated boost.

Results: Mean total patient time in treatment room was 14 minutes. Mean heart dose was $<$ 0.2 Gy and mean lung dose $<$ 1 Gy. Most patients experienced grade 1 dermatitis, and 2 with grade 2. With a mean follow up time of 25 months, 3 patients had minor dry skin in the treatment area and no other late toxicities or problem with the breast implant. All patients self-reported 'good to excellent' cosmetic outcomes. No patients had evidence of local failure.

Conclusions: Single field IMPT is a safe, feasible and effective approach for APBI in early stage breast cancer patients with breast augmentation.

PTC58-0116

Dosimetric comparison of intensity modulated proton therapy (IMPT) versus volumetric modulated arc therapy (VMAT) on early stage left breast cancer

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Purpose/Objectives: To evaluate the dosimetric impacts of IMPT as compared with VMAT using photon on early stage left-sided breast cancer.

Materials and Methods: Six early stage left-sided breast cancer patients treated by post-lumpectomy irradiation with 4 partial arcs VMAT were retrospectively re-optimized using IMPT. One single left anterior oblique IMPT field was used for optimization using Varian Eclipse proton TPS. In both IMPT and VMAT planning, simultaneous integrated boost technique was used to give 58 Gy(RBE) to GTV (tumor bed) and 50 Gy(RBE) to PTV (whole left breast) in 25 fractions, assuming RBE of 1.1 and 1 for proton and photon, respectively. GTV and PTV coverage, dose conformity and homogeneity were reported by dose received by 95% and 98% target volumes ($D_{95,}$ D_{98}), conformity number (CN) and homogeneity index (HI). Mean dose (D_{mean}), near-maximum dose (D_2), percentage organ volume receiving more than 5, 10, 20 Gy(RBE) (V_{10},V_{20},V_{30}) of heart, contralateral breast, left and right lungs were compared. D_{mean}, D_2, $V_{30,}$ $V_{40\ and}$ V_{50} of skin (a layer structure of 2mm inward from the body contour on irradiated side) were also evaluated. Statistical analysis was performed using Wilcoxon-signed rank test. A two-tailed $p<0.05$ was considered statistically significant.

Results: All results were tabulated in Table 1.

Conclusion: Higher skin dose was observed in IMPT, but it could significantly lower doses to heart, contralateral breast, left and right lungs while provided better target coverage and comparable conformity and homogeneity as compared with 4 partial arcs VMAT in post-lumpectomy left-sided breast cancer.

PTC58-0197

A treatment planning study for bilateral breast irradiation comparing intensity modulated proton therapy to 3D and intensity modulated photon therapy

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Objective: Delivery of irradiation in women with bilateral breast conserving surgery represents a technical challenge. The purpose of this study was to compare IMPT to single isocenter bilateral tangential 3D conformal fields combined with IMRT (3D/IMRT) and VMAT in bilateral breast radiotherapy.

Methods: IMPT plans, 3D/IMRT and VMAT photon plans were created for 5 patients with synchronous bilateral breast cancer. The conventional dose (50Gy/25f to whole breast and 60Gy/25f to tumor bed) was delivered. The 3D/IMRT plans used 8-11 fields, including 4 tangential ones; Only one field was delivered in VMAT plans; for IMPT, fields were used in 5°, 20° and 340°, 355° to avoid motion uncertainties.

Results: IMPT and VMAT plans conferred higher target volume coverage as compared with 3D/IMRT ($p=0.0079$ for tumor bed, 0.037 for whole breast). V107 were 13.7±4.8%, 0.4±0.4% and 0.56±0.40% for tumor bed and 25±2.4%, 22.69±2.2% and 13.1±4.3% for the breast subtract tumor bed using 3D/IMRT, VMAT and IMPT. The results of Dmean and V20Gy of lungs using 3D/IMRT(9.3±0.4Gy and 17.2±0.9%) and VMAT(10.26±0.8Gy and 15.9±1.9%) were comparable, while it was lower in IMPT plan(2.6±0.7Gy and 4.6±1.1%). The meanV5Gy in VMAT plans(44.9±3.4%) were the highest while it was still the lowest in IMPT plans(12.5±2.1%). Also, VMAT resulted in highest Dmean to heart(7.6±0.6Gy) than 3D/IMRT(5±1.1Gy) and IMPT(0.52±0.3Gy). Doses for left anterior descending coronary artery were significantly decreased as well using IMPT(Fig.1).

Conclusion: IMPT provides improved homogeneity with excellent sparing of surrounding normal structures. Lower doses for lungs and heart were higher using VMAT compared to either IMPT or 3D/IMRT.

PTC58-0443

Dosimetric evaluation of proton beam radiotherapy for clinically gross internal mammary lymph node metastasis in breast cancer

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Purpose: Radiotherapy targeting of breast cancer internal mammary lymphadenopathy is challenging. Our purpose was to report target coverage and organs at risk (OAR) dosimetry of intensity modulated proton therapy (IMPT) for the treatment of breast cancer with clinically gross internal mammary lymph node (IMN) metastases.

Methods: We identified patients with breast cancer and clinically-involved, unresected IMN metastases treated with lumpectomy or mastectomy followed by IMPT with IMN boost at our institution between 2015 and 2018. Patients with other sites of unresected regional lymph node disease were excluded.

Results: Ten eligible women were identified. Mean age was 47.9 (R: 38-65). Nine of 10 patients were left-sided. Nine of 10 patients were clinical T2-T3. Nine patients were clinical N3b and 1 patient was clinical N2b. Surgery was mastectomy in 9 and lumpectomy in 1. The clinical target volume (CTV) included the chest wall or breast and axillary, supraclavicular, and IMNs, and was treated to a median dose of 50 Gy (RBE 1.1) in 25 fractions with one patient receiving a sequential chest wall boost to 60 Gy. All patients received a boost to un-resected IMNs. Median IMN boost dose was 5625 cGy (R: 5375- 6000) delivered as a simultaneous integrated boost in 9 patients. Table 1 lists the CTV coverage for the IMN boost and OAR.

Conclusion: For the treatment of clinically gross IMN metastases in breast cancer, radiotherapy boost with IMPT provides exceptional target coverage and normal tissue sparing.

PTC58-0576

Monoisocentric intensity modulated proton therapy technique for bilateral chest wall and regional nodal radiotherapy

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Purpose: To report a novel monoisocentric technique to deliver bilateral chest wall and comprehensive nodal radiotherapy using IMPT.

Methods and Materials: Patient, RC, is an 83 y.o. female with bilateral breast cancer ER/PR+, Her-2 -, post bilateral mastectomy, axillary dissection, with right breast pmT2N1 2.5 cm invasive ductal carcinoma, 2/19 +LNs; left breast pT2N2a IDC 3.4 cm 6/12 + LNs. Adjuvant IMPT was delivered to the bilateral chest walls, axillary, supraclavicular and internal mammary lymph nodes on the right side. The prescribed dose was 50.4 Gy (RBE) in 28 fractions. An IMPT plan was generated using a single isocenter without any couch rotation or shift to maximize delivery efficiency. The plan was robustly optimized with multiple field optimization using three fields-AP, LAO and RAO. In between the fields, gradient junctions of approximately 8 cm were created to improve setup robustness (Fig1). Non-ionizing surface imaging was used for initial patient set up and intra-fraction motion monitoring.

Results: The heart mean dose was 0.06 Gy with total lung V20Gy and V5Gy of 8% and 21%. Total CTV D99% was 50.4 Gy in nominal plan, and 47 Gy in the worst-case scenario (5 mm setup errors and 3.5% range uncertainty) in robustness evaluation. For daily patient setup, the Intra-fraction motion monitored by the surface imaging was within 3.5 mm variations (Fig2).

Conclusions: This monoisocentric, IMPT approach is a novel and highly efficient technique to deliver bilateral chest wall and comprehensive nodal radiotherapy with favorable target coverage, cardiac and lung sparing.

Clinics: Lung

PTC58-0204

Commercial vs. in-house developed IMPT treatment planning system for lung cancer: a treatment planning comparison

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Purpose: To compare intensity-modulated proton therapy (IMPT) plans generated by our in-house developed treatment planning system (TPS) (Solo^{TM}) and the commercial TPS (cTPS) for lung cancer.

Methods and Materials: We selected 10 lung cancer patients. Two IMPT plans were created using Solo^{TM} and cTPS. The plans were designed to deliver the prescription doses to internal target volumes (ITV) on averaged 4D-CTs. Solo^{TM} plans were imported back to cTPS and recalculated to get the final dose distributions in cTPS for fair comparison. Both plans of each patient were further verified in CT_0 and CT_{50} phases and all plans met the clinical requirements. Plan robustness on all phases was quantified using dose-volume-histograms (DVH) band method. Interplay effects were evaluated by the in-house developed software for every plan, which randomized starting phases of each field per fraction. DVH indices were compared using Wilcoxon rank sum test.

Results: Compared to plans generated by cTPS, in nominal scenario Solo^{TM} plans delivered significantly lower esophagus $V_{60Gy[RBE]}$ and D_{mean}, and cord D_{max} with better robustness in target coverage, homogeneity, hot spots, and lung D_{mean}. In CT_0 and CT_{50} phases, Solo^{TM} plans had better ITV dose coverage and cord D_{max} with comparable robustness. In term of interplay effects, Solo^{TM} plans had statistically better target dose coverage, and lower esophagus D_{mean} and cord D_{max}.

Conclusions: Solo^{TM} generated IMPT plans of higher quality, and comparable or better plan robustness in all phases and interplay effects. Our study supports the usage of Solo^{TM} to design IMPT plans for lung cancer patients.

PTC58-0226

Mitigation of interplay effects with layer repainting techniques in intensity modulated proton therapy for early stage non-small cell lung cancer

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Ten patients with early staged NSCLC were enrolled and 4D robust IMPT treatment plans were performed. In the development of treatment plans, the uncertainties of Monte Carlo dose engine were 0.5% and dose grid resolution was 3mm; setup and range uncertainties were 5mm and 3%, respectively. We applied layer repainting techniques with different numbers of repainting (3, 4, 5, 6, 7 times) and evaluated differences in the mitigation of interplay effects. We evaluated the treatment plans withT50 as the reference CT, and all other CTs were aligned to T50 using hybrid deformable method. 4D static dose was the accumulated dose on all the phases. To assess the 4D dynamic dose, we simulated the respiratory cycles with T50 as the starting phase, recalculated the doses on 10 phases continuously, and accumulated the doses to T50. In order to evaluate interplay effects, we calculated the difference of DVH indices between 4D static dose and 4D dynamic dose for CTV and lungs. Due to interplay effects, the mean values of target coverage, conformity and homogeneity index reduced by 14.0%, 12.6% and 23.8%, respectively. The mean values of lung V5Gy[BRE] and V20Gy[RBE] improved by 3.1%, 2.1% and 2.9%.With all different of layers repainting, mean values of target coverage, conformity and homogeneity index could be increased but was still in lower 5% compare with 3D dose. In addition, average values of lung V30Gy[RBE] improved by 2.4%, 2.7%, 4.9%, 4.4%, and 4.4%, respectively. This study reveals that IMPT is not suitable for early staged NSCLC only use repainting.

PTC58-0260

Protons increases BED compared with photons in partial stereotactic ablative boost radiotherapy for large NSCLC

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Purpose: Photons Partial Stereotactic Ablative Boost Radiotherapy (P-SABR) is able to achieve high local control rate while keeping the side effect well tolerated in large NSCLC (diameter >5cm) according to our previous research. We also find that larger tumor volume receiving high BED could increase local control in radiotherapy. This study aims to further explore whether protons can elevate the tumor volume receiving high BED compared with photons.

Methods: We planned 30 patients who previously received P-SABR with photons for large NSCLC. The patients underwent repeat planning for intensity-modulated proton beams (2-3 beams) ("IMPT" for short), proton arc beams (10-14 beams to simulate ARC) ("PAT" for short) and photon IMRT, VMAT plans. P-SABR plans were described before. GTV boost is the max volume receiving SABR and the protons plans were created to achieve comparable RBE of GTV margin to photons plans. Dosimetric variables were acquired in both proton and compared photon plans.

Result: Both IMPT and PAT could achieve higher B_{90} (the ration of volume of BED>90Gy to the in-field tumor), B_{100} and B_{110} than photons plans($P<0.05$). D_{75} (volume of the structure receiving RBE >75 GyE), $D_{80,}$ D_{85} and D_{90} were also larger for proton than for photon P-SABR($P<0.05$). In addition, despite the RBE for esophagus were similar ($P>0.1$), protons plan could significantly reduce the RBE for other OARs ($P<0.05$).

Conclusion: Larger tumor volume receiving high BED was achieved by protons compared with photons. Protons P-SABR might increase the local control rate while reducing the side effect for large NSCLC.

PTC58-0656

Proton radiotherapy to improve non-small cell lung cancer outcomes: Two clinical study proposals

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Background: There is limited supporting evidence for proton radiotherapy in non-small cell lung cancer (NSCLC); thoracic proton radiotherapy research is required.

Objective: We propose two clinical studies which will likely be the UK first clinical proton radiotherapy studies and the first translational thoracic proton radiobiology program.

Clinical study 1

Concurrent chemoradiotherapy followed by durvalumab is the new standard-of-care in stage III NSCLC. Preclinical evidence supports that proton radiotherapy has higher tumor immunogenic and lower normal tissue immunosuppressive effects, compared to photon radiotherapy.

Design: Randomized proof-of-concept biomarker study (n=66).

Main hypothesis: Baseline and longitudinal immune-related biomarkers (tissue & blood) provide data on differences between proton and photon radiotherapy/ immune interactions.

Secondary hypotheses:

1. Proton radiotherapy increases adjuvant durvalumab initiation secondary to reduced toxicity and non-inferior tumor control, compared to photon radiotherapy
2. Protons reduce cardiac morbidity from thoracic radiotherapy, as quantified using longitudinal cardiac biomarkers (cardiac CT, echocardiography & blood)

Clinical study 2

Locoregional recurrence after (chemo)radiotherapy is common in NSCLC and could be salvaged with a repeat radiotherapy course. Photon re-irradiation is associated with significant toxicity. Targeting tumor hypoxia, which is associated with radiotherapy resistance and poor survival, could improve NSCLC outcomes.

Design: Single arm 2-stage proof-of-concept study (n=40).

Main hypothesis: Proton re-irradiation is safe in recurrent NSCLC.

Secondary hypotheses:

1. Nimorazole (a hypoxic radiosensitizer) improves patient survival when added to proton re-irradiation, without increasing radiotherapy-related adverse-events
2. Hypoxia biomarkers (imaging & tissue) predict benefit from nimorazole
3. Patient reported outcome measures reduce thoracic re-irradiation morbidity and mortality

PTC58-0689

Photon vs proton therapy for reduction of cardiac toxicity in locally advanced lung cancer using the model-based approach

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Purpose/Objective: To identify a sub-group of patients with locally advanced lung cancer who would benefit from proton beam therapy (PBT) compared to photon therapy for reduction of cardiac toxicity using the model-based approach.

Material and Methods: Volumetric modulated arc photon therapy (VMAT) and robust-optimised intensity modulated proton therapy (IMPT) plans were generated to a physical dose of 70Gy in 35 fractions. Cases were selected to represent varying anatomical locations of primary tumor and nodal involvement (15/20 had nodal involvement). Contouring and treatment planning followed RTOG-1308. Dose to the heart and sub-structures were compared. Risk estimates of grade 3+ cardiac toxicity were calculated based on models which incorporated dose metrics and patients' risk-factors.

Results: There was no statistically significant difference in target coverage between VMAT and IMPT. Overall IMPT delivered lower doses to the heart (mean, V5 and V30). In VMAT plans, there were statistically significant positive correlations between heart dose and thoracic vertebral level that coincided with the lower limit of the tumor. Between VMAT and IMPT, there was no statistically significant difference in dose to the heart or sub-structures when disease (primary and nodes) extended above T7 vertebrae. When disease extended to and below T7 vertebrae IMPT delivered lower doses to the heart and sub-structures (mean, V5 and V30, $P<0.001$). Risk estimates for cardiac toxicity for these patients are presented in Table 1.

Conclusion: Patients with tumor extension to and below T7 vertebrae are likely to benefit most from proton over photon therapy. The absolute benefit is higher in patients with underlying cardiac disease.

Clinics: GI

PTC58-0726

Re-irradiation of rectal and anal cancer with intensity modulated proton therapy (IMPT) and endo-rectal balloon

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Background: Treatment management is challenging in patients with local recurrence of anal-rectal cancer (LR-ARC) who had received previous radiation therapy. We described our clinical experience using IMPT and endo-rectal balloon for the re-irradiation of these patients which had partial circumferential tumor recurrence.

Methods: Seven patients of LR-ARC with less than 2/3 of the circumference involvement, treated at Scripps Proton Therapy Center were selected. EUS was done for depth and circumference involvement. Trans-rectal debulking of tumor was encouraged. Patients were set up in the supine position and the Radiadyn ImmobiLoc endo-rectal balloon (ERB) is used and inflated with water to as big the volume as patient could tolerated. All patients underwent CT and MRI based simulation. GTV is defined as tumor seen on CT/MRI/PET scan, and CTV is defined as GTV with a 5 mm margin. No elective nodal volumes were treated. Daily fraction of 1.8-2 Gy for 50.4 to 54 Gy to the CTV and 56-60 Gy to GTV given simultaneously. Treatment was delivered with 1-2 beams. All patients had daily orthogonal kV x-rays and CBCT, weekly adaptive plan, and concurrent chemotherapy.

Results: All patients finished treatments, and none had $>$ grade 2 rectal toxicity. With a mean follow up time of 29 months, 5 of 7 patients still alive. 3 patients with CR, 2 with PR, and 3 with PD. One immunocompromised (HIV) patient had grade 3 ulceration requiring hyberbaric oxygen and wound care.

Conclusion: Re-irradiation using IMPT and ERB in selected patients is technically feasible with acceptable toxicity.

PTC58-0378

Short-course preoperative pencil beam proton therapy for rectal cancer: A pilot study

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Purpose: To evaluate the feasibility, dosimetry, and complications of short-course preoperative proton beam therapy for rectal cancer.

Materials and Methods: From October 2018 to January 2019, 2 male patients with Stage III rectal cancer planned by short-course preoperative radiotherapy were included in this study. The dose of radiotherapy was 25 CGE/5 fractions. Pencil beam proton therapy system (Sumitomo Heavy Industries) using single-field uniform dose (SFUD) was delivered through 2 posterior oblique fields (135 and 215 degree). Doses of pelvic bone marrow, small bowel, and penile bulb were calculated using RayStation 6.0 planning system. Image-guided cone beam CT was used before each treatment. Acute toxicities of radiotherapy were evaluated by common toxicity criteria (CTC) version 4.

Results: Dosimetries of pelvis bone marrow (V2.5=45.9±12.0% vs. 85.6±9.1%; V5=40.4±10.5% vs. 79.6±9.8%; V7.5=35.8±8.6% vs. 75.7±10.3%; V10=29.7±4.9% vs. 62.8±7.9%), small bowel (V10=58.6±39.3 mL vs. 142.9±94.0 mL; V15=50.3±34.3 mL vs. 73.9±37.4 mL; V20=41.5±28.4 mL vs. 47.3±30.6mL), and penile bulb (mean dose=6.4±1.7 CGE vs. 12.1±1.3 CGE) were better than VMAT planning. One patient completed proton therapy then received surgery within 1 week. No Grade 1 or greater leukopenia, dermatitis and diarrhea were noted before or after operation.

Conclusion: Short-course preoperative pencil beam proton therapy for rectal cancer is feasible because of better dosimetries of pelvic bone marrow, small bowel, and penile bulb. Further prospective study is considered for short-term and long-term outcomes.

PTC58-0575

ProtOeus: Consideration of interplay effects for the proposed oesophageal trial

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Background: Neoadjuvant chemoradiation prior to definitive surgery in locally advanced oesophageal cancer has shown improved outcomes in the CROSS trial. However, the anatomical position, size and proximity of the tumor to surrounding structures, poses a conundrum as there is a high integral dose to neighbouring organs, which may translate to an increased perioperative risk and worse long-term outcomes. The aim of ProtOeus is to test the validity of this hypothesis.

Methods: In preparation for the UK-based trial - ProtOeus, a comparison of treatment plans with photons and protons was made in a patient with 'flip-flop' oesophageal tumor. The interval target volume (ITV) was delineated over ten 4DCT phases. A three-beam posterior oblique single field optimisation (SFO) plan was created on the maximal exhalation phase (MEP). Velocity 4.0 was used to study the effect of respiratory motion and change in water equivalent thickness (WET). The nominal proton plan with repainting was recalculated and the dose was deformed back to MEP. The effect of interplay was studied by taking into account spot delivery time and breathing rate.

Results: Target doses between photons and protons were comparable, but reduced dose to the heart, liver and lung with protons. Doses to the tumor and organs at risk (OARs) are relatively unaffected in ten different simulated starting points of respiratory cycle.

Conclusion: The initial results are promising that protons may have a potential role in reducing dose to surrounding structures. We will be exploring this approach further with Monte Carlo planning dose calculations and validate it with other cases.

PTC58-0397

Functional liver imaging for hepatotoxicity risk prediction in primary liver cancer patients with cirrhosis treated with proton therapy

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Background: There is an unmet need for objective and radiotherapy modality specific metrics for mitigating radiation-induced liver disease (RILD) in primary liver cancer (PLC) patients with cirrhosis. We hypothesize that [^{99m}Tc]-sulfur colloid (SC) SPECT/CT can provide global and spatial metrics for improved RILD-risk stratification in patients treated with proton therapy (PT).

Methods: We retrospectively reviewed 47 patients treated with PT with Child-Pugh (CP)-A (68%) or CP-B/C (32%) cirrhosis that underwent pretreatment SC SPECT/CT scans. SC SPECT imaging was mined for intensity threshold-based functional liver volumes (FLV), mean liver-spleen uptake ratio (L/S_{mean}), and total liver function ($TLF = FLV*L/S_{mean}$). Cox regression was performed for correlation to RILD-specific survival (RILD-SS) and overall survival (OS) and logistic regression for correlation to CP-score 2+ and/or grade 3+ liver enzymes (CP+2/LFTs).

Results: Baseline CP-score ($p=0.003$) and functional liver parameters of FLV ($p=0.023$), L/S_{mean} ($p=0.003$), and TLF ($p=0.003$) were significant univariate predictors of RILD-SS, but not CT-derived anatomic dosimetric metrics. Risk stratification using $TLF > 0.65$, representative of high global liver function, into low and high-risk subgroups predicted for a 100% vs 17% 1-year RILD-SS ($p<10E-6$). Functional liver imaging metrics remained independently associated with RILD-SS when adjusting for CP-score. Global metrics of TLF ($p=0.013$) and L/S_{mean} ($p=0.040$) were superior predictors of RILD-SS relative to CP-score ($p>0.6$). Whereas baseline CP-score was the only significant factor for CP+2/LFTs prediction ($p=0.016$), functional liver metrics retained significance when evaluating for OS.

Conclusions: Baseline functional imaging liver metrics improved hepatotoxicity risk prediction in PLC patients treated with PT.

PTC58-0460

Is a squamous cell carcinoma (SCC) of the anus indeed a reasonable target of proton beam radiotherapy (PBT)?

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Chemoradiotherapy is a standard treatment for anal SCC. Myelotoxicity often results in treatment interruptions. For IMRT a grade 3-4 myelotoxicity occurs in up to 61%. Pencil beam scanning (PBS) PBT significantly decreases the doses in bone marrow (BM), bladder, small intestine, hip joint. The efficacy, toxicity and dosimetric data were analysed to assess the role of PBT.

PBS PBT was administered in 21 patients with anal SCC, stage T2N0M0–T4N3M0. Simultaneous integrated boost has been used in all patients – PTV-1, tumor with margin and involved lymph nodes 57,5 GyE, PTV-2 regional lymph nodes 45 GyE, both in 25 fractions, 5 fractions/week. Concomitant chemotherapy: CDDP+capecitabine.

The prescribed dose was administered in all patients. Median follow-up is 25 months. Chemotherapy was reduced in 3 patients. The median of $V10_{GyE}$ in BM was 64%. Medians of D_{mean} in abdominal cavity, bladder and hip joints were 13,8 GyE, 12,74 GyE, and 24,8 GyE respectively. The acute toxicity was predominantly mucocutaneous, gr.3 24%, diarrhoea, gr.3 9,5%, 1 episode of neutropenia gr.4 (not febrile) and 1 gr.3. A treatment interruption (2 d) required in 1 pt. 6 pts. (28,5%) developed late radiation proctitis gr. 2 (5 pts.) gr. 3 (1 pt.), median onset 6 months. Complete regression was achieved in 19 pts, 1 salvage surgery, 1 salvage chemotherapy was required.

The acute toxicity is moderate, predominantly cutaneous. Myelotoxicity is mild, maintaining continuous treatment course. Late radiation proctitis poses the most serious complication. A good efficacy and favourable toxicity profile related to excellent dosimetry supports PBS PBT for anal SCC.

PTC58-0218

PIOPPO TRIAL: Phase 2 study for preoperative treatment of operable or borderline operable adenocarcinoma with chemotherapy and carbon ion hadrontherapy

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Introduction The purpose of PIOPPO trial is to assess the role of neoadjuvant chemotherapy followed by carbon ion hadrontherapy (CIRT) for patients (pts) with resectable (rPC) or borderline resectable pancreatic cancer (brPC). Primary endpoint is local PFS and secondary endpoints are OS, R0-resectability rate and treatment toxicity (including intra and perioperative toxicity).

Methods: PIOPPO is a prospective, phase II, multicenter and single-arm study. Thirty patients will be enrolled in the study. Sample size has been defined with an expected probability of success proportion of success at 24 months of 60% vs 35% (H0: $p <= 0.35$-H1: $p > 0.35$). Enrolled patients, with a rPC/brPC, underwent to 3 cycles of FOLFIRINOX followed by CIRT (total dose:38.4 Gy [RBE], 8 fractions, 4 fractions per week). 4D and breath gated planning is performed and rescanning is carried out. GTV is established using CT, MRI and PET. CTV is GTV with 5 mm margin, locoregional elective lymph node and neuroplexus region. From 4 to 6 weeks after completion of CIRT pts will undergo conventional pancreatic surgery. Subjects who meet the enrolment criteria but decline to participate in the study will serve as controls. Adjuvant chemotherapy is given according to clinical practice.

Results: Since January 2018 five patients have been so far enrolled and four have completed the surgical phase. No significant acute toxicities, including surgery-related have been observed.

Conclusions: Our first experience is promising and CIRT does not affect negatively the surgical approach. The combined treatment of PIOPPO trial for rPC/brPC is safe and feasible.

PTC58-0222

Clinical impact of re-irradiation with carbon ion radiotherapy for locally recurrent rectal cancer

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Purpose: The re-irradiation (reRT) of locally recurrent rectal cancer (LRRC) presents challenges due to the proximity of critical organs such as bowel. Carbon ion radiotherapy (CIRT) could be a treatment option for conventionally difficult-to-cure patients (pts)

Aim: to evaluate safety and efficacy of reRT with CIRT in previously irradiated LRRC pts

Patients and Methods: Between 2014 and 2017, 10 pts were treated with CIRT as reRT for LRRC at CNAO. All pts had a history of surgery for RC and pelvic radiotherapy (in one case radiotherapy was delivered for prostatic cancer). At time of the first recurrence, 1 pt underwent to reRT with stereotactic radiotherapy. Three pts received surgical spacer implantation to keep bowel apart for the tumor.

Results: Patient, tumor and treatment details are summarized in Table I. All patients completed the treatment. Acute toxicity was mild and mainly neuropathy (G2:10%; G1:20%). Median follow-up was 13 months. We observed 20% of G2 late peripheral neuropathy. No G$\geq$3 acute/late reaction nor pelvic infections were reported. Four pts experienced local progression after CIRT (median disease-free survival: 11.4 months). Three pts experienced systemic progression. The estimated 1-year-local control rate was 80%.

Conclusion: reRT with CIRT for LRRC appears to be safe and effective with an acceptable rate of morbidity of normal tissue. More data and longer follow-up are required to investigate the long-term disease control and to determine late effects.

PTC58-0009

The effectiveness of proton beam therapy for liver metastatic recurrence in gastric cancer patients

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Background: Liver metastasis from gastric cancer (LMGC) is a noncurable, fatal disease with a 5-year survival rate of $<$10%. Proton beam therapy (PBT) is expected to be an effective therapeutic method for LMGC. The purpose of this cross-sectional study is to evaluate the safety and efficacy of PBT.

Methods: The consecutive patients who underwent PBT from 2010 to 2015 were isolated from institutional database. Patients with extrahepatic metastatic lesions were excluded. The effectiveness was assessed local control (LC), overall survival (OS) and progression-free survival (PFS). Adverse events were described according to the Common Terminology Criteria for Adverse Effects version 4.03.

Results: Seven patients were enrolled. The median diameter of target lesions was 31 mm (13–68). The most frequent dosage was 72.6 Gy (RBE) in 22 fractions. All patients completed PBT without interruption. The median follow-up period was 41.7 months (20.7–66.3). The 3-year LC rates was 85.7%. The 3-year OS rates was 68.6%. The 3-year PFS rates was 43%. No grade 3 or more severe adverse events were observed.

Conclusions: The PBT might be one of options for patients with liver metastasis of gastric cancer.

PTC58-0257

Proton and carbon ion radiotherapy for locally advanced pancreatic carcinoma: A preliminary report

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Background: To evaluate the clinical outcome of proton and carbon ion radiotherapy (CIRT) for locally advanced pancreatic carcinoma (LAPC).

Methods and Materials: From Jun 2015 to Oct 2018 41 LAPC patients from 3 prospective clinical trials were combined together for this analysis. 16 patents received proton/photon followed by CIRT (proton/photon plus CIRT) with total doses of 46.2GyE to 68.4GyE by 1.8GyE to 3GyE per fraction, and 25 patients, CIRT alone of 51GyE to 62.9GyE by 3.5GyE to 3.7GyE per fraction. The overall survival (OS), progression-free survival (PFS), local progression-free survival (LPFS) and distant metastasis-free survival (DMFS) and acute/late toxicities were analyzed.

Results: With a median follow-up of 13.9 months, for all patients, the median survival time was 18.2 months, and OS, LPFS, PFS and DMFS at 12-month and 18-month were 82.5% and 52.4%; 75.5% and 56.8%; 63.4% and 39.5%; 83.1% and 60.7%, respectively. CIRT alone yielded significantly improved LPFS at 18-month as compared to proton/photon plus CIRT (85.9% vs. 33.8%, p=0.025), but no significant differences in OS, PFS and DMFS were observed between proton/photon plus CIRT and CIRT alone. One patient experienced grade 3 gastrointestinal ulceration. No other severe acute or late toxicities were observed.

Conclusion: CIRT alone improved LPFS significantly, as compared to proton/photon plus CIRT. The toxicity of Proton/photon plus CIRT and CIRT alone for LAPC was mild and tolerable.

Clinics: GU

PTC58-0205

Re-irradiation using particle therapy for pelvic recurrence of gynecological cancer

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Introduction: Reirradiation (reRT) of recurring gynecological tumors (RGT) of the pelvic area presents challenges due to the high cumulative dose in normal tissues such as bowel.

Aim: to evaluate safety and efficacy of reRT with particle therapy (PT) for pelvic RGT.

Material and Methods: Between May 2014 and December 2018, 9 patients (pts) with RGT were admitted for PT at CNAO. Pt and treatment characteristics were summarized in Table I. Two patients, with marginal lymph node recurrence, were irradiated with protons up to a total dose of 25 Gy RBE and 51 Gy RBE, respectively. The remaining women underwent to carbon-ion radiotherapy (CIRT) with a median total dose of 50.4 Gy RBE (range: 36-57, median number of fractions: 12). Five patients with pelvic side wall recurrences received surgical spacer placement to keep intestinal tracts apart from the tumor.

Results: All patients completed the planned treatment and no acute toxicities (CTCAE 4.0) G>2 were observed. For the evaluable patients, no G≥ 2 late toxicity was reported. For pts with a follow-up ≥ 3 months, median LC was 7 months (range: 3-13,8), median MFS was 4.2 months (range: 3-14,2) and median OS was 7 months (range: 3-14,2). 1 pt experienced local progression and 4 pts died for systemic progression. Data is still ongoing.

Conclusions: Although the study's limitations, PT showed no severe toxicities for recurrence of gynecological cancers after RT. Further research is required to identify long-term safety and efficacy for a larger number of pts.

PTC58-0208

Carbon ion radiotherapy in the management of the melanoma of the lower genital tract

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Background: Malignant mucosal melanoma (MMM) has been regarded as radioresistant tumor.

Aim: to report preliminary results with carbon ion radiotherapy (CIRT) for gynecological MMM treated at CNAO.

Patients and Methods: Between 2016 and 2018, 9 patients (pts) were admitted for CIRT. Patient and tumor characteristics are described in Table I. CM and VuM patients were irradiated with up to a total dose of 28 GyRBE in 3 fractions and 68.8 GyRBE in 16 fractions, respectively, to CTV defined as the GTV + uterine cervix and corpus for the CM and GTV + vulva for the VuM. For VaM the small pelvic space including GTV was irradiated with up to a total dose of 38.7-43 GyRBE followed by a GTV boost of up to a total dose of 68.8 GyRBE in 16 fractions. One pt underwent to adjuvant CIRT on the small pelvic space (43 Gy RBE) after radical surgery without lymphadenectomy.

Results: Treatment was well tolerated and no interruption was needed. Acute toxicity was mild. No G≥2 (according to CTCAE 4.0) late toxicities were observed. Overall, for pts with a follow-up≥ 3 months, the median LC was 8.75 months (< for VuM and CM), the median MFS was 5.25 (range: 3-22,83) and the median OS was 7.03 (range: 3-25,83). 3 pts died for systemic progression. Data is still ongoing for the latest enrolled pts.

Conclusions: CIRT is a safe non-invasive option treatment for gynecological MMM. Clinical trial with a longer follow-up and larger series of patients is necessary.

PTC58-0010

Treatment time and irradiation dose of organs at risk changes using spot deletion operation in prostate cancers

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Purpose: To investigate how long treatment time is reduced and how much irradiation dose of organs at risk if using spot deletion operation in the intensity modulated proton beam therapy (IMPT) planning in prostate cancers.

Methods: Simulation study was performed in 10 prostate cancer patients. After IMPT planning was completed to accomplish dose restriction in our institute, spots were deleted. One method is lower energy spots were automatically deleted step by step (protocol A) and another method is spots which were distant from the prostate gland were manually deleted step by step (protocol B). Dose distribution of the prostate gland was scheduled as 63 Gy(RBE) with 21 fractions. Both methods were continued within the range of clinical target volume irradiated at least 60 Gy(RBE) was 100%. Treatment time and dose distribution of rectum and bladder was examined.

Results: Treatment time reduction was 2.1—17.5 (median 17.7) seconds in protocol A and 6.3—49.2 (24.3) seconds in protocol B. Rectum volume irradiated at least 50 Gy(RBE) increase was 0.04—1.3 (0.4)% in protocol A and -6.3—-0.7 (-3.1)% in protocol B. Bladder volume irradiated at least 50 Gy(RBE) increase was -0.2—0.3 (0.08)% in protocol A and -4.1—-0.9 (-2.5)% in protocol B.

Conclusions: Spots deletion which distant from the prostate gland operation is efficient in the reduction of not only treatment time but also irradiation dose of organs at risk.

PTC58-0441

Proton therapy for prostate cancer: Favorable outcomes with low toxicity profile

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Purpose: To prospectively evaluate outcomes for treatment of prostate cancer at a single institution

Method: We reviewed patients with localized prostate cancer treated definitively at a single institution, from 10/2010 thru 2/2017. Patients were followed prospectively on a multi-institutional trial (Proton Collaborative Group registry trial), with patient and physician reported outcomes. Fiducial markers were used in all patients, with rectal immobilization used for nearly all patients (free rectal water in 385, rectal balloon in 342, and hydrogel interstitial spacer in 220). Median dose was 79.2 Gy(RBE) in 44 fractions, with 102 patients receiving 70 Gy(RBE) in 28 fractions and 51 with SBRT doses of 38 Gy(RBE) in 5 fractions.

Results: 952 patients were treated, 272 with Stage I (AJCC7, low risk), 467 Stage IIA (intermediate risk), 196 Stage IIB (high risk) and 17 Stage III. Median followup is 50 months, with a minimum of 18 months. 32 patients have died, only 5 from prostate cancer. Adverse events have been mostly grade 1-2, with 9 patients with Grade 3 GU toxicity and 4 patients with grade 3 GI toxicity.

Conclusion: Proton beam therapy is an effective and well tolerated treatment for localized prostate cancer.

PTC58-0647

Gastrointestinal toxicity is significantly less with hydrogel compared to other rectal immobilization techniques

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Background: Rectal toxicity including rectal hemorrhage is a known side effect of radiation therapy for prostate cancer. Interstitial hydrogel provides both rectal immobilization and provides spacing between the prostate and rectum, and should reduce the incidence and severity of rectal toxicity.

Methods: Patients with localized prostate cancer were treated with definitive proton beam therapy at a single institution on a multi-institutional registry protocol (PCG Registry). Patients were treated primarily with lateral fields to a dose of 79.2 Gy(RBE) in 44 fractions (762 patients), 70 Gy(RBE) in 28 fractions (102 patients) or 38 Gy(RBE) in 5 fractions (51 patients), using fiducials and daily stereoscopic imaging for localization. Patients were treated in consecutive cohorts with rectal water (100 cc), rectal balloons (60-90cc) and hydrogel, and followed prospectively for late (>90 days after treatment) adverse events.

Results: 947 patients treated from 10/10 through 2/17, with median follow-up of 4.4 years, minimum 1.5 years. Rectal water (RW) was used in 385 patients, rectal balloons (RB) in 342 patients and hydrogel spacer (HS) in 220 patients. Post-treatment grade 3 toxicity was rare in all groups. The grade >2 overall GI toxicity rate was 14.8% for RW, 17.3% for rectal balloons, but only 2.2% for HS. Grade 2 rectal bleeding of any grade was noted in 10.4% for RW, 12.3% for RB, and 2.2% for HS.

Conclusions: Interstitial hydrogel spacer significantly reduced the post-treatment gastrointestinal toxicities from radiation therapy, including a significantly lower risk of any rectal bleeding.

PTC58-0293

Dosimetric comparison between CyberKnife and pencil-beam scanning proton therapy in stereotactic ablative radiotherapy for prostate cancer

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Purpose: To compare dosimetric difference between CyberKnife M6 and pencil-beam scanning proton therapy (PBSPT) in stereotactic ablative radiotherapy (SABR) for prostate cancer.

Materials and Methods: Four CyberKnife plans from patients with prostate cancer treated by the same radiation oncologist were selected. Their DICOM images of computed tomography-simulation were used for PBSPT plans with single-field optimization of opposed lateral fields. The patient preparation, prescribed dose and constraints in CyberKnife plans followed the protocol of RTOG 0938 trial, and those in PBSPT plans mostly followed the protocol of PCG-GU002-10 trial but lacking rectal balloon and prescribing the same dose with CyberKnife plans (36.25Gy in 5 fractions). We compared the dosimetry of planning target volume (PTV), rectum, bladder and urethra.

Results: The PBSPT plans had significantly lower conformal index (1.08 vs 1.31, p=0.031), new conformal index (1.14 vs 1.33, p=0.047), maximum and mean doses in PTV (37.71Gy vs 40.89Gy, p=0.034; 37.21Gy vs 38.19Gy, p=0.027), dose of 95% PTV volume (99.86% vs 101.18%, p=0.016), and volumes of 105% and 100% prescribed dose in PTV (0% vs 52.98%, p=0.013; 94.52% vs 98.55%, p=0.007). There was no significant difference of dosimetry in rectum. The PBSPT plans had lower mean dose in bladder and maximum dose in urethra but had larger volumes of 95%, 90% and 80% prescribed dose in bladder.

Conclusion: The PBSPT plans had better conformality and homogeneity, lower mean dose in bladder and maximum dose in urethra, but worse PTV coverage by 100% prescribed dose and larger volumes of high percentage-prescribed dose in bladder.

PTC58-0409

Proton vs. carbon ion radiation therapy: A retrospective study of prostate cancer treatments at the Heidelberg Ion-Beam Therapy Center

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The Heidelberg Ion Therapy Center (HIT) opened its doors in 2009, treating nearly 400 patients with either proton or carbon ion beams to combat prostate cancer-related disease. Since then, several treatment regimens were applied differing in fractionation scheme and tissue radio-sensitivity factor (α/βratio), used in the local effect model (LEM) during biological dose optimization for carbon ion treatments. With nearly a decade of clinical indication, what have we learned about relative biological effectiveness (RBE) for proton and carbon ion beams and the impact of physical and biophysical parameters on treatment outcome?

In this work, the first HIT prostate patient cohort from the prospective randomized phase 2 clinical trial (Ion Prostate Irradiation, IPI) was collected to study biological effect in context of tumor control. The 92 IPI patients received either proton or carbon ion therapy with identical fraction regime and prescription dose in the target, a total dose of 66 GyRBE administered in 20 fractions. Forward calculations yielding physical dose, dose-averaged linear energy transfer (LET_d) and effective dose (applying LEM-IV) are performed using HIT's fast dose engine FRoG (Fast dose Recalculation on GPU) developed in-house. For improved prediction of actual delivered dose, computation is performed using the original planning CT as well as weekly control CTs to account for anatomical changes throughout the treatment course (Fig. 1). Biophysical uncertainty in prostate cancer treatment planning and delivery is investigated to assess clinical efficacy of the two particle therapy modalities.

PTC58-0161

Hydrogel spacer injections for prostate cancer patients undergoing proton beam therapy

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Background: Various studies have evaluated the efficacy of hydrogel spacer in prostate cancer treatment and have demonstrated that hydrogel spacer is useful and safe. Meanwhile, various anesthetic techniques are used for its injection, and the related pain, regarded as an associated problem, has not been studied in detail.

Methods: This survey was conducted on 200 prostate cancer patients who received hydrogel spacer injections. After local anesthesia was applied to the perineum (20 mL of 1% lidocaine), a gold marker each was placed with a 22-gauge needle via the transperineal approach. Then, the fat between the prostate and rectum was punctured with an 18-gauge needle, and hydrodissection was performed using physiological saline; this was followed by an injection of 10 mL of hydrogel spacer composed of polyethylene glycol. Immediately after completion of the procedure, the degree of the pain severity was rated on pain scales and recorded by the patients themselves. The numerical pain scale (0-10) was used to assess pain severity.

Results: Hydrogel spacer injections were successfully administered to all 200 patients. The median and mean pain scores were 5 and 5.2. At completion of the procedure, hypotension due to vagal reflex was observed in 10 patients. In all these patients, blood pressure recovered after only a few minutes of rest.

Conclusion: Although hydrogel spacer injection before proton beam therapy for prostate cancer is a safe procedure, it often causes moderate pain that lasts for a short period of time.

PTC58-0496

The role of 99mTc-labeled PSMA-SPECT/CT and mfMRI in the prediction of early response after carbon ion therapy for prostate cancer

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Purpose: The purpose of this study was to assess the predictive value of 99mTc-labeled PSMA-SPECT/CT and Apparent Diffusion Coefficient of MRI for predicting treatment response after carbon ion therapy in prostate cancer.

Methods and Materials: A total of 26 patients underwent 99mTc-labeled PSMA-SPECT/CT and multi-parametric MRI before and after carbon ion therapy. The mean apparent diffusion coefficient (ADC_{mean}) and tumor/background ratio (TBR) were measured on the tumor and the percentage changes between 2 time points (ΔADC_{mean} and ΔTBR) were calculated. Based on follow up clinical examinations, patients were divided into two groups: good response (PSA level $<$ 0.2ng/ml after 6-month treatment) and poor response (PSA level $\geq$0.2ng/ml after 6-month treatment).

Results: The median follow up time is 27.9 months. The ADC_{mean} was significantly increased compared with the pretreatment value($p< 0.001$), while the TBR was significantly decreased compared with the pretreatment value(p=0.001). The ΔADC_{mean} and ΔTBR were negatively correlated with each other (Spearman correlation coefficient, -0.586; $p = 0.002$). On ROC curve analysis for predicting treatment response, the area under the ROC curve (AUC) of ΔTBR (0.867, 95% confidence interval [CI], 0.686, 1.000) for predicting good response was higher than than ΔADC_{mean} (0.819, 95% confidence interval [CI], 0.631, 1.000). The optimal critical for distinguishing good response from poor response in the ROC analysis were $\Delta TBR \leq$ -25.5% and $\Delta ADC_{mean} >$ 59.9%, respectively.

Conclusions: Our preliminary data indicate that the changes of ADC_{mean} and TBR maybe an early bio-marker for predicting prognosis after carbon ion therapy in patients with prostate cancer.

PTC58-0137

The adverse events of carbon ion radiotherapy with different segmentations for prostate cancer in China: From 23/24 to 16 fractions

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Purpose: To assess the effects of two different dose fractionation regimens on radiation toxicity and biochemical control in prostate cancer treated with carbon ion radiotherapy (CIR).

Materials and Methods: A total of 94 prostate cancer patients treated with CIR between June 2014 and March 2018 were analyzed. The incidence of adverse events was assessed based on the Common Terminology Criteria for Adverse Events version 4.0. Biochemical failure was analyzed, based on Phoenix definition (nadir+2.0ng/ml) in the patient subgroups that received each dose fractionation.

Results: Grade 1 morbidities of the genitourinary (GU) system in 23/24-Fx and in 16-Fx patients were observed in 16 (43.24%) and 8 (14.04%) patients, respectively, while grade 2 (G2) morbidities of the GU were observed in 3 (8.11%) and 9 (15.97%) patients, respectively. No>G2 GU toxicities were observed during the follow-up period. The incidence of GU toxicity in patients treated with 16 fractions was lower than that in patients treated with 23/24 fractions(P=0.03). Grade 1 rectal haemorrhage occurred with 23/24-Fx and with 16-Fx in 2 patients (5.41%) patients and 1 patient (1.75%), respectively. No ≥G2 rectal toxicities were observed. Rectal toxicities did not differ significantly between 23/24-Fx and 16-Fx. There was no significant difference in biochemical failures between 16 Fx(0 patients) and 23/24-Fx (3 patients; 2 were diagnosed with pathologies) (P=0.56).

Conclusion: CIR of 59.2/60.8 GyE in 16-Fx may reduce the incidence of genitourinary toxicity compared with 23/24-Fx. CIR hypofractionation regimens for prostate cancer were considered feasible. An analysis of long-term outcomes is warranted.

PTC58-0557

Preliminary exploration of clinical factors affecting acute toxicity and quality of life after carbon-ion therapy for prostate cancer

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Purpose: To present acute toxicity and quality-of-life after carbon ion radiotherapy (CIRT) in the Shanghai Proton and Heavy Ion Center (SPHIC) and identify the clinical factors that influenced urinary, bowel, sexual and hormonal function.

Methods: Sixty-four patients with prostate cancer admitted from July 2015 to January 2018 received locoregionally CIRT. At baseline and 5 time-points after radiotherapy, we assessed patients' quality-of-life using the EPIC-26 Chinese version. Logistic regression was performed to identify the clinical factors associated with acute GU toxicity and quality-of-life.

Results: There were 13(20.3%) Grade 1 and 7(10.9%) Grade 2 acute GU events, as well as 2 (3.1%) cases of Grade 1 acute GI toxicity in all. Urinary irritative/obstruction quality-of-life had temporary declines at the end of CIRT (-7.92±1.76, p<0.001). And bowel QOL had a clinically relevant decline at 2 years follow-up. As for urinary incontinence and sexual domain, the quality of life remained stable all the time within 2 years after CIRT. TURP was a risk factor that predicted a decline in urinary related quality-of-life. Age made a difference to bowel quality-of-life. As for sexual quality-of-life, castration status was a remarkable risk factor. IPSS≥8 increased 5.3-fold risk of Grade 1-2 acute GU toxicity. 66 GyE/24Fx had higher occurrence of GU toxicity than 59.2 GyE/16Fx, and bladder's DVH parameters might account for this.

Conclusion: Treated with carbon-ion radiotherapy, prostate cancer patients had low acute radiation-related toxicity and superior quality-of-life. Several clinical factors were found to be related to quality-of-life declines and acute GU toxicity.

Clinics: Sarcoma - Lymphoma

PTC58-0055

First-in-human phase I study of space modulated particle therapy using bioabsorbable spacer

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Background: Surgical spacer placement (SSP) is useful in particle therapy (PT) for patients with abdominal or pelvic tumor adjacent to the intestines. We have developed bioabsorbable spacer which degrades by hydrolysis. We conducted a first-in-human phase I study of the combination of SSP and PT (space modulated particle therapy) using bioabsorbable spacer.

Methods: Eligibility criteria included histologically proven abdominal or pelvic tumor adjacent to the intestines, no metastasis, and no previous radiotherapy. Periodic CT images were obtained before SSP and before/during/after PT (until the spacer disappeared). Treatment planning was performed for each CT image set (until the end of PT) and doses for PTV and OARs were analyzed. Thickness of the spacer was measured for each CT image set. Adverse events were evaluated according to CTCAE v4.0.

Results: Five patients were enrolled in this study. Three patients had sacral chordoma, 1 patient had sacral MPNST, and 1 patient had retroperitoneal leiomyosarcoma. All patients received 70.4 Gy (RBE) (proton therapy in 3 and carbon ion therapy in 2). $V_{95\%}$ of PTV before SSP, at the beginning of PT, and at the end of PT was 82.1±11.3%, 98.1±1.1%, and 97.1±0.8%, respectively. The spacers maintained enough thickness (≥1 cm) at the end of PT and disappeared within 8 months after SSP in all patients. No ≥grade 3 adverse events were observed.

Conclusions: SSP using bioabsorbable spacer was useful and safe in PT for abdominal or pelvic tumors adjacent to the intestines. Larger prospective studies with a longer follow-up are warranted.

PTC58-0495

Carbon ion radiotherapy for extracranial chordoma or chondrosarcoma: Initial experience from Shanghai Proton and Heavy Ion Center

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Particle therapy, especially carbon ion radiotherapy (CIRT) is deemed to be a promising treatment for chordoma and chondrosarcoma. We retrospectively analyzed the outcomes of patients with extracranial chordoma or chondrosarcoma treated by CIRT at Shanghai Proton and Heavy Ion Center to evaluate the efficacy and safety of this promising treatment method. Between May 2015 and April 2018, 21 consecutive patients with chordoma (n=16) or chondrosarcoma (n=5) treated by CIRT were enrolled. Local control (LC), progression free survival (PFS) and overall survival (OS) rates were estimated through the Kaplan-Meier method. The association between each of the candidate prognostic factors and the estimated LC, PFS or OS was tested with the log rank test. The median gross tumor volume (GTV) was 512.7 ml (range, 142.6-2893.0 ml). The median prescription dose was 69 gray equivalent (GyE) (range, 57–80 GyE). After a median follow-up of 21.8 months (range, 7.2-39.2 months), the 1-year LC, PFS and OS were 93.8%, 88.4% and 100%, respectively, whereas the 2-year LC, PFS and OS were 85.2%, 80.4%, 100%, respectively. Univariate analysis revealed that age, mental implant status, treatment status, sex, dose, and GTV were not significant prognostic factors for LC, PFS or OS. No grade 2 or higher early and late toxicities were observed within follow-up. CIRT can provide efficient tumor control for patients with extracranial chordoma or chondrosarcoma. Long-term results deserve further investigation, even in a prospective randomized trial.

PTC58-0261

Proton therapy for cardiac sarcoma: A two-case series describing the clinical and dosimetric advantages of proton-based therapy

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Cardiac sarcomas are extremely rare neoplasms with an aggressive behavior. Surgery is the most accepted treatment modality, but total resection is rarely achievable without causing fatal damage to the heart. The purpose of this study was to describe our experience implementing intensity modulated proton therapy (IMPT) for cardiac sarcomas.

We present two patients who received IMPT. The first patient was 55-year-old woman with pleomorphic sarcoma of right ventricle, spreading to pulmonary valve, tricuspid valve and ventricular septum with metastatic spread to mediastinal lymph nodes. The GTV was treated to 66 Gy in 2,2 Gy per fraction. The CTV, including affected mediastinal lymph nodes was irradiated to 60 Gy, using simultaneously integrated boost technique.

The second patient was a 15-year-old boy with pericardial Ewing sarcoma. The CTV was irradiated to 55,8 Gy.

CT scans, MRI scans and treatment were made using respiratory gating at end expiration.

The follow-up period for the first patient is 3 months and for the second patient 4 months. There was no any acute toxicity during treatment and follow-up. CT and MRI scans three months post-radiation demonstrated tumor shrinkage in both cases.

In order to compare dose values, IMRT photon-based plans were generated. IMPT produced lower mean lung dose, lung V5 and V20, heart V40, and dose to contralateral lung than did IMRT.

IMPT in combination with respiratory motion tracking appears to be a technically feasible and clinically well-tolerated local control modality for cardiac sarcomas, providing limited exposure to organs at risk in comparison with IMRT photon plans.

Clinics: GI / Sarcoma Poster Discussion Sessions
PTC58-0371

Preliminary clinical observation of particle radiotherapy for 20 cases of thymic malignancies and dosimetric comparison between photon and particle plans

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Objective: To evaluate the safety and efficacy of particle therapy (PT) for thymic malignancies, and to compare dose distribution between photon versus particle radiotherapy.

Methods: From 09/2015 to 08/2018, 20 patients with thymic malignancies (stage I-IVB) who were treated with PT using pencil beam scanning technique and≥1 time of follow-up were enrolled. The median maximum diameter was 6.1 (2.7-17.7) cm for the 14 patients with gross tumors. Prescriptions of proton 44-48.4GyE/20-22 fractions with carbon ion boost 21-23.1GyE/7 fractions were administered to patients with gross tumor except one palliative treatment, proton 45-61.6GyE/25-30 fractions to patient after R0/R1 resection, and carbon ion 60GyE/20 fractions for re-irradiation. Dosimetric comparisons were conducted in patients with gross tumors using the same total dose of 66Gy(E).

Results: The median follow up time is 12.6 (2.4-36.3) months. Only one local recurrence was observed (6.8 months after start of treatment) in the palliatively-treated patient who had huge lesion after failure of multiple regimens of chemotherapy. Regional lymph node, pleural or distant metastasis occurred in 3 patients 6.1∼22.8 months after treatment. One patient developed a second primary cancer confirmed by histological pathology 13.7 months after the start of treatment. Except one myocardial infarction (grade 4 late toxicity), no other toxicities ≥grade 3 were observed. Compared with photon, particle plans could significantly reduce the doses to lungs, heart, esophagus and spinal cord.

Conclusion: PT was safe and effective for patients with thymic malignancies after short-time follow-up, and has significant advantages over photon in sparing organs at risk.

PTC58-0649

Clinical outcome of sacral chordoma patients treated with pencil beam scanning proton therapy

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Purpose: To analyze tumor control and toxicity in sacral chordoma patients treated with definitive or postoperative pencil beam scanning (PBS) proton therapy (PT).

Methods and Materials: Sixty patients with histologically proven sacral chordoma treated between November 1997 and October 2009 at the Paul Scherrer Institute either by postoperative (n=50) or definitive PT (n=10) were retrospectively analyzed. Survival rates were calculated using the Kaplan-Meier actuarial method. The log-rank test was used to compare different functions for local control (LC), freedom from distant recurrence (FFDR) and overall survival (OS). Acute and late toxicity was assessed according to the Common Terminology Criteria for Adverse Events v5.0.

Results: Median follow-up was 48 months (range, 4-186). Local recurrence occurred in 20 (33%) patients. At 4 years, LC, FFDR, and OS rates were 77%, 89%, and 85%, respectively. In univariate analysis, subtotal resection (P=0.02) and gross tumor volume > 130 ml (P=0.04) were significant predictors for local recurrence. Twenty-four (40%), 28 (47%), 8 (11%) patients experienced acute Grade 1, Grade 2, and G3, respectively. Grade 2 and 3 late toxicity was observed in 27 (45%) and 9 (15%). No grade 4-5 late toxicity was observed.

Conclusion: Our data indicate that PBSPT is both safe and effective. Subtotal resection and gross tumor volume are prognostic factors for local tumor control.

PTC58-0628

Acute and late skin toxicity assessment in paediatric/young adult patients with Ewing's sarcomas treated with chemo-radiotherapy

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Purpose: To assess skin toxicity for paediatric patients/young adults with Ewing's Sarcomas (ES) treated with chemo-radiotherapy.

Materials and Methods: Thirty-four patients with stage I-IV ES in different sites treated between 2010 and 2017 were retrospectively analysed. Eleven patients received Proton Beam Therapy (PBT) within the "Overseas Program" and 23 external radiotherapy with Photons (XRT) at the Christie. Median age at diagnosis was 15.5 years (4–25). All patients received chemotherapy regimens containing Doxorubicin or Actinomycin D (figure1). Radiotherapy doses were given in 1.8 Gy per fraction in various total doses (45, 50.4, 54 and 59.4 Gy). Acute and late toxicities were recorded using RTOG/EORTC scoring system.

Results: The risk of developing acute (grade 1 versus higher than grade 1) and late (grade 0 versus grade non-zero) skin toxicities was measured against known clinical factors by employing logistic regression. There were no significant differences on developing acute/late skin toxicities based on different primary sites of the disease or between PBT and XRT groups. Moreover, risk of developing acute/late skin toxicity didn't associate with chemotherapy regimens. No correlation was found between the severity of acute/late toxicity and total dose. However, risk of developing late skin toxicity was significantly higher for patients treated with surgery (p=0.02).

Conclusions: No differences in terms of skin toxicity was found for patients treated with chemo-radiotherapy using either PBT or XRT. Associations between dosimetric parameters and skin toxicity will be considered in the future.

PTC58-0724

Early experience with protons for chordomas of the sacrum and mobile spine

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Background: We report on our early experience with pencil beam scanning proton radiotherapy for chordomas of mobile spine and sacrum.

Methods: Retrospective review of 31 patients treated between June 2015 and January 2019. The mean age was 59 (range 22-88) with 22 men. Records were reviewed for tumor outcomes and toxicity.

Results: Sixteen tumors were sacrococcygeal and 15 were mobile spine including 6 cervical, 3 thoracic, and 6 lumbar. Twelve sacrococcygeal tumors had definitive radiation with a median dose of 69.6 Gy RBE1.1 in 30 fractions (73.8 Gy3 EQD2). The median size of sacral tumors was 7.6 cm (range 2.6 – 16) with 8 patients having disease extending to S1 or S2. All but two patients with mobile spine lesions underwent surgery with 3 having an en bloc resections in combination with radiation and 10 had partial or piecemeal resections, most of these having surgery elsewhere before presenting to our institution. Two patients also received a dural P-32 plaque treatment at the time of resection. Three of the spine patients were treated with a component of photon therapy in a preoperative setting prior to surgical resection. With a median follow-up 13.3 months (0-37.7), all patients except one who sustained a compression fracture and biopsy at the time of vertobroplasty revealing active disease are locally controlled. No myelopathy has been reported. Data on acute complications and other outcome data will be presented.

Conclusions: Early results of pencil beam scanning treatment for chordoma of mobile spine are promising and consistent with expected outcomes.

PTC58-0071

S-1 and concurrent image-guided proton therapy for unresectable locally advanced pancreatic cancer: An interim report of phase II study

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Background: We designed single-institutional prospective phase II trial to assess the efficacy and safety of chemo-proton therapy (CCPT) with image-guided proton therapy (IGPT) for unresectable locally advanced pancreatic cancer (LAPC). The present study reports the interim results of the trial.

Materials and Methods: Between February 2015 and March 2018, 22 patents with unresectable LAPC received CCPT followed by adjuvant chemotherapy. Metallic markers were used for image guidance using a respiratory-gated imaging technique. Proton therapy with 60 GyE/ 20 Fr was delivered to the GTV and 40 GyE/20 Fr to the CTV, using a field-in-field technique. Patients received concurrent and adjuvant S-1 chemotherapy. Toxicities were evaluated according to CTCAE version 4.0.

Results: Median patient age was 72 years (range; 50-79) and the male: female ratio was 10:12. Eleven patients had a pancreatic head tumor. Three had positive lymph nodes. All patients completed CCPT plus adjuvant chemotherapy. The median follow-up was 14 months. Local control (LC) and overall survival (OS) rates at 1-year were 100% and 81%, respectively and 2-year were 89% and 34%, respectively. The median OS was 19 months. Acute grade 3 toxicities observed were anemia in 4 patients (18%) and anorexia in 2 patients (9%) and grade 2 were gastric ulcer in 2 patients (9%). Chronic grade 3 was anemia in 3 patients (14%).

Conclusions: CCPT with our protocol for unresectable LAPC was generally well tolerated without patients uncompleted the treatments. It appeared to offer good LC. Further investigation with a larger number of patients is warranted.

PTC58-0024

Two-years clinical experience of the carbon-ion pencil-beam fast rescanning for the treatment of hepatocellular carcinoma

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Purpose: In November 2016, our center started carbon-ion radiotherapy (CIRT) for hepatocellular carcinoma (HCC), which has respiratory motion. The feature of our CIRT is the combination of carbon-ion pencil-beam fast rescanning (CI-PBFR) and the gating with a respiratory sensor to overcome interplay-caused inhomogeneous dose distribution. We reviewed clinical outcomes of HCC patients treated by this distinctive method at our center.

Methods: Between November 2016 and December 2017, 27 patients with HCC were treated with the combination of CI-PBFR and the gating with a respiratory sensor. All patients were treated at a total dose of 60 Gy (RBE) in 4 fractions. Overall survival (OS) and local control (LC) were estimated by Kaplan-Meier method. Adverse Events (AE) were evaluated according to Common Toxicity Criteria for AE version 4.

Results: Median follow-up time was 15.5 months (range, 3.0 to 24.3 months) from the start of CIRT. Mean age was 74 (range, 63 - 92). Twenty-five patients (92.6%) were Child-Pugh class A and two patients (7.4%) were class B. Mean tumor size was 3.8 cm (range, 1.0 - 11.2) in diameter. 1-year OS and LC were 92.1% and 95.5%, respectively. Grade 3 AE was observed in two patients (7.4%): increased transaminase and pleural effusion. Grade 4 or higher AE was not observed.

Conclusion: The combination treatment of CI-PBFR and the gating with a respiratory sensor was feasible for HCC, which has respiratory motion. This method is a promising high precision therapy with tolerability and effectiveness for HCC.

PTC58-0112

The effectiveness and role of risk-adapted proton beam therapy for hepatocellular carcinoma

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Purpose: To evaluate the effectiveness and role of risk-adapted proton beam therapy (PBT) in patients with hepatocellular carcinoma (HCC).

Methods and Materials: A total of 243 HCC patients received risk-adapted PBT with three dose-fractionation regimens (regimen A [n=40], B [n=60], and C [n=143]) according to the proximity of their gastrointestinal organs ($<$1 cm, 1–1.9 cm, and $\geq$2 cm, respectively): the prescribed doses to planning target volume 1 (PTV1) were 50 GyE (EQD2, 62.5 GyE_{10}), 60 GyE (EQD2, 80 GyE_{10}), and 66 GyE (EQD2, 91.3 GyE_{10}) in 10 fractions, respectively, and those of PTV2 were 30 GyE (EQD2, 32.5 GyE_{10}) in 10 fractions.

Results: In all patients, the 5-year local recurrence-free survival (LRFS) and overall survival (OS) rates were 87.5% and 48.1%, respectively, with grade $\geq$3 toxicity of 0.4%. In regimens A, B, and C, the 5-year LRFS and OS rates were 54.6%, 94.7%, and 92.4% ($p<0.001$), and 16.7%, 39.2%, and 67.9% ($p<0.001$), respectively. The 5-year OS rates of the patients with mUICC stages I, II, III, and IVA and BCLC stages A, B, and C were 69.2%, 65.4%, 43.8%, and 26.6% ($p<0.001$), respectively and 65.1%, 40%, and 32.2% ($p<0.001$), respectively. In a multivariate analysis, the Child-Pugh classification, alpha-fetoprotein level, mUICC stage, dose-fractionation regimens, and primary tumor response were independent prognostic factors associated with OS.

Conclusions: PBT could achieve promising long-term tumor control and have a potential role as a complementary or alternative therapeutic option across all stages of HCC.

PTC58-0123

A preliminary report of a phase I dose escalation study: Scanning carbon ion beam radiation therapy for hepatocellular carcinoma

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Purpose: To analyze the dose limiting toxicities (DLTs) in hepatocellular carcinoma (HCC) patients treated with scanning carbon ion beam radiation therapy (SCIRT).

Methods and Materials: Patients diagnosed as HCC, surgical unresectable or refusal to surgery, were treated by SCIRT with 4 dose levels of 55 GyE, 60 GyE, 65 GyE and 70 GyE in 10 fractions, respectively (5 fractions per week). At least 3 patients would be enrolled in each dose level. Once the observation time was less than 3 months for the last enrolled patient in the 2nd to 4th dose level, a new eligible patient would be assigned to the dose level, which was one level lower than that was testing. When >33% of the patients developed DLTs, the dose escalation would be terminated.

Results: From Jan 2016 to July 2018, 23 patients have been enrolled in this study with median diameter of 5.1 cm, 5 in dose of 55GyE, 6 in 60GyE, 9 in 65GyE and 3 in 70GyE. All the patients completed SCIRT and no treatment-related DLTs occurred. For acute toxicities, grade 1-2 of early skin injury, leokocytopenia, neutrocytopenia and thrombocytopenia were observed in 13.1%, 26.1%, 17.4% and 17.4% patients, respectively. None of patients presented treatment-related late toxicities. Median follow-up time was 16.0 months. The 1-and 2-year overall survival rates were 95.2% and 89.9%, and the 2-year local progression-free survival rates were 100%.

Conclusion: SCIRT with treatment dose of 70GyE in 10 fractions is safe for HCC patients, and survival and local control were promising.

PTC58-0334

Early results of re-irradiation for rectal cancer using pencil-beam scanning proton therapy are promising

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Purpose: Re-irradiation (Re-RT) for rectal cancer (RC) in patients with prior pelvic RT has been shown to be safe and effective. However, limited data exists with the use of proton therapy (PT). We hypothesize that PT is a safe and feasible for re-treatment and may allow for decrease in toxicity or treatment escalation.

Methods and Materials: We performed a single institutional retrospective IRB-approved analysis of all RC patients with any prior pelvic RT re-irradiated with Pencil-Beam Scanning proton therapy (PBSPT). We collected patient and treatment characteristics, including prior diagnosis, re-irradiation records, and toxicities. Outcomes, including overall Survival (OS) and Local Control (LC), were estimated using Kaplan-Meier.

Results: Twenty-three patients (median follow-up 17 months) received PBSPT Re-RT from 2016-2018: 14 patients w/ recurrent RC [median prior dose 50.4 Gy (43.2-63.0)] and 9 patients w/ de novo RC and variable prior RT (8 for prostate, 1 for ovarian). Median Re-RT dose was 48 Gy [(16.0-60.0); 17/23 were treated BID], and 21/23 received concurrent chemotherapy. Four underwent surgical resection (all R0). Three patients experienced grade 3 acute toxicities, and no acute Grade 4-5 toxicities were observed. Two patients had grade 3+ late toxicities, including a grade 5 toxicity occurring in a patient with history of significant injury from prior RT. One-year LC and OS were 83.3% (95% CI 72.1-94.5%) and 77.6% (95% CI 67-88.2%), respectively.

Conclusion: In this largest such series, early results of PT for Re-RT for RC are promising, with longer follow-up needed.

PTC58-0470

Pathologic complete response (pCR) rates and outcomes after neoadjuvant chemoradiotherapy with proton or photon radiation for distal esophageal adenocarcinoma

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Background: Pathologic complete response (pCR) after neoadjuvant chemoradiotherapy is associated with improved survival in patients treated for esophageal cancer. While proton beam therapy (PBT) has demonstrated reduced toxicities, limited reports have evaluated pCR rates between modalities.

Methods: Single-institutional review of patients from 2016-2018 with distal esophageal adenocarcinoma treated with trimodality therapy including PBT was undertaken; patients were compared 2:1 to patients treated in a contemporary timeframe with photons.

Results: Sixteen consecutive proton patients were compared to 32 consecutive photon patients. Overall median follow-up was 20 months. All patients received concurrent chemotherapy with carboplatin/paclitaxel. Median radiation dose in both cohorts was 50.4/1.8Gy (p=0.353). Age, gender and race were well balanced, but patients treated with PBT were more advanced stage (p=0.049) with increased nodal burden (N2: 31% PBT vs. 3.0% photon, p=0.019). Despite this, proton patients achieved an equivalent proportion of nodal clearance (64% PBT vs. 67% photon, p=0.873). pCR rates did not significantly differ between modalities (19% PBT vs. 25% photon, p=0.627).

Two grade 5 perioperative complications occurred in the photon group; no PBT patients experienced a grade 5 event. There were no differences in grade 3/4 toxicities. 18-month survival was comparable between PBT and photon patients (88% CI, 76 to 100 vs. 71% CI, 62 to 80; p=0.288).

Conclusions: The use of PBT in trimodality therapy for distal esophageal adenocarcinoma is safe and yields pCR rates comparable to photon radiation and historical controls. pCR and nodal clearance rates did not significantly differ despite PBT patients having higher AJCC stage and nodal burden.

Clinics: Head and neck

PTC58-0058

BNCT for head and neck cancer: Summary of reactor irradiation

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Purpose: Boron Neutron Capture Therapy (BNCT) is a form of radiation therapy that utilizes alpha rays from thermal neutron capture of the boron atom. In this report, we summarize our clinical results for BNCT for the treatment of head and neck cancer at our institution.

Methods: We started clinical studies for the treatment of head and neck cancer in 2003. Since then, we have completed the following four clinical studies: (1) an analysis of the accumulation of BPA in the tumor and surrounding normal -tissue using an ^{18}FBPA-PET study, (2) a BNCT clinical trial for recurrent head and neck cancer, (3) a BNCT clinical trial for head and neck melanoma, and (4) a BNCT clinical trial for newly diagnosed advanced head and neck cancer.

Results: The ^{18}FBPA-PET study showed no difference in the T/N ratio between an SCC and a non-SCC group. Overall, 83% of the patients had a T/N ratio of more than 2.5. The response rates were more than 80% for all the BNCT clinical studies. Although mild alopecia, xerostomia, and fatigue were observed in all the patients, no severe adverse effects of grade 3 or higher occurred in these patient series (Fig.1).

Conclusions: Our preliminary results demonstrated that BNCT is a potentially curative therapy for patients with head and neck cancer. The treatment does not cause any serious adverse effects, and can be used regardless of whether the primary tumor has been previously treated.

PTC58-0383

Intensity-modulated proton therapy reduces acute treatment-related toxicities for patients with nasopharyngeal cancer: A case-control propensity score match study with VMAT

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Purpose/Objective(s): To evaluate the differences in the treatment-related toxicity and neutropenia rate between patients with nasopharyngeal cancer treated with IMPT and VMAT.

Materials and Methods: From December 2016 to December 2017, 80 patients receiving IMPT and 80 patients receiving VMAT for nasopharyngeal cancer were propensity score-matched. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE 4.03) was used for toxicity evaluation. Chi-square test was used in the univariate analysis. Then multivariate logistic regression analysis was used in the multivariate analysis for binary toxicity endpoints.

Results: The median follow-up time was ten months. During treatment, 5 IMPT-treated patients (6.3%) and 13 VMAT-treated patients (16.3%) were suffered from nasogastric tube insertion (OR=0.386, P=0.045). The mean duration of NG-tube placement was 2 and 6.4 weeks in the IMPT and VMAT patients respectively (P=0.318). The patients with body weight loss over 8 % were significantly different between IMPT group 20% and VMAT group 35% (OR=0.571, P=0.034). Of the patients treating with concurrent chemo-radiotherapy, there were significantly less any grade neutropenia adverse events in IMPT group compared with VMAT group (OR=0.324, P=0.023). There were seven patients (10.3%) in IMPT group and twelve patients (17.7%) in VMAT group not receiving cisplatin dose intensity over 200 mg/m2. After allowing potential confounders in multivariate analysis, IMPT treatment retained its independent association with NG-tube insertion and weight loss over 8% (P=0.039).

Conclusion: IMPT is associated with reduced rates of NG-tube insertion, weight loss over 8% and neutropenia adverse events. The result may potentially increase treatment outcome for nasopharyngeal cancer patients treated with IMPT.

PTC58-0298

Proton therapy boost in locally advanced head and neck cancer: Toxicity and clinical outcome

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Purpose: feasibility, acute toxicity and clinical outcome in patients (pts) with LAHNC treated with exclusive sequential mixed beam (MB) approach: IMRT followed by proton therapy (PT) boost

Methods: between July 2012 to January 2018, 41 pts with histologically proven LAHNC (stage III-IV) were treated with MB approach: IMRT of the neck and macroscopic disease followed by PT boost on the pre-treatment macroscopic disease. Tumor sites were: nasopharynx 28 pts (69%), oropharynx 5 pts (12%), larynx 1 patient (2%), sinonasal 4 pts (10%) and oral cavity 3 pts (7%). IMRT prescription dose was 54-60 Gy (elective irradiation of the neck and macroscopic disease), PT prescription dose was 10-20 Gy RBE, for a total dose up to 70-74 Gy RBE. Local control (LC) and toxicity profile (according to CTCAE V4.03- scale) were evaluated.

Results: The median follow-up was 12 months. Treatment was well tolerated, 11 (27%) pts developed G3 acute radiation-related toxicity: 2 pts (5%) mucositis, 1 patient (2%) skin reaction and 5 pts (12%) dysphagia. No pts had high grade (G3-4) late toxicity. LC was 83%. Four pts had local recurrence at 12, 11, 8 and 8 months after treatment, respectively. Three pts developed distant metastases at 6, 18 and 25 months after the end of the treatment. Three pts died for tumor specific-causes.

Conclusions: for pts with LANHC a MB approach was feasible and our results showed good short-term outcome and limited radiation-related side effects. Preliminary results are encouraging but a longer follow-up and large patient accrual are required

PTC58-0300

Toxicity in patients with locally advanced nasopharyngeal cancer treated with mixed beam (IMRT and proton therapy boost)

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Objective: Compare radiation-induced acute toxicity in patients (pts) affected by LANPC treated with sequential IMRT and proton therapy (PT) boost (mixed beam-MB) with an historic cohort of pts treated with IMRT.

Materials and Methods: From June 2012 to November 2017, 27 pts with LANPC (cT3-4) were treated with MB approach: IMRT up to 54-60 Gy followed by PT boost up to 70-74 Gy RBE. This cohort were compared to an historic cohort of 17 pts treated with IMRT only. Pts treated with IMRT only received a total dose of 69.96 Gy. The acute-toxicity profile (worst event) was evaluated according to CTCAE V4.03 scale.

Results: The total dose was significantly higher (p=0.02) in pts treated with MB. G3 mucositis and G2 xerostomia were found in 11% and 76% (p=0.0002) and 7% and 35% (p=0.02) of pts treated with MB and IMRT, respectively. Absorbed dose to acute toxicity-related structures were summarized in Table1. For MB cohort median follow-up was 25 months. All but one pts achieved complete tumor response and no pts developed local/regional recurrences. For IMRT only cohort median follow-up was 51 months. One patient died for treatment-related toxicity. One patient did not achieve a complete tumor response. Three patients experienced tumor local progression; 3 pts experienced also lymph node recurrences/metastasis.

Conclusions: Our results suggest that sequential MB approach for locally advanced NPC pts is safe with an excellent acute toxicity profile. Preliminary results on clinical outcome are encouraging but need to be confirmed in lager cohort of pts.

PTC58-0676

Proton therapy for head and neck cancer – how much actual evidence is there for benefit? A 'devil's advocate' view

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There is only a limited literature in the use of proton or carbon ion therapy in head and neck cancer (HNC) and this has dealt mainly with addressing the physics and dosimetric challenges involved and optimization of both proton and carbon ion delivery and optimizing patient selection. There have been less than 30 papers in the literature in the last five years, dealing with the clinical use, outcomes and benefits of proton therapy in head and neck cancer, when compared to intensity modulated radiotherapy or arc techniques..

Past literature reviews have emphasized the potential for proton therapy, but the use of protons to boost photon therapy in earlier protocols, and the paucity of prospective randomized controlled trials in HNC, (an exception, the NCT0189 3307 prospective trial, but with no results until after 2023), give a mixed and imprecise view of proven outcome benefits for the use of protons or carbon ions, in the common head and neck cancers.

This presentation summarizes the positive clinical outcomes, described for HNC, treated with proton or carbon ion therapy, and illustrates which subsites may benefit most with proton treatment from the present literature, and, as importantly show where there is no positive data. With the development of the UK proton service, some HNC patients will have considerable distances to travel to access these innovative treatments, and it is important to describe the evidence base, showing which patients may benefit, and how, depending on specific HNC subsites and be aware where there is no evidence of outcome benefit.

PTC58-0227

Inter-fraction robustness of intensity-modulated proton therapy in the treatment of post-operative oropharyngeal squamous cell carcinomas

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Purpose: To evaluate dosimetric consequences of inter-fraction set up variation and anatomical changes in patients receiving multi-field optimised (MFO) intensity modulated proton therapy for post-operative oropharyngeal cancers.

Methods: Six patients treated with proton beam therapy for postoperative oropharyngeal cancer were evaluated. Plans were optimised to clinical target volumes (CTVs) with parameters of 3 mm setup and 3.5% range uncertainty. Each patient underwent weekly online cone-beam computed tomography (CBCT). Planning CT was deformed to the CBCT to create virtual CTs (vCTs) on which the planned dose was recalculated. vCT plan robustness evaluation was evaluated using a set up uncertainty of 1.5 mm and range uncertainty of 3.5%. Target coverage, $D_{95\%}$, and hotspots $D_{0.03cc}$, were evaluated for each uncertainty along with the nominal, error-free, plan. Mean dose to organs at risk (OAR) for the nominal plan and relative % change in weight from baseline were evaluated.

Results: Robustly optimized plans in post-operative oropharyngeal patients using a single CT scan are robust against inter-fraction set up variations and range uncertainty. Max $D_{0.03cc}$ in the nominal plans were clinically acceptable across all plans. No patients lost $\geq$10% weight from baseline, Figure 1. Mean dose to the ipsilateral parotid gland, oral cavity, larynx, pharyngeal constrictor muscles and max dose to the spinal cord remained within tolerance, Figure 2.

Conclusion: MFO plans in post-operative oropharyngeal patients were robust to inter-fraction uncertainties in set up and range in regard to CTV coverage. A robust analysis protocol for MFO plans will improve consistent reporting and plan evaluation amongst radiotherapy centers.

PTC58-0701

A comparison of physician and patient reported outcomes in the elderly head and neck cancer population: IMPT vs. IMRT

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Dosimetric comparison of head and neck radiation plans between intensity modulated radiotherapy (IMRT) and intensity modulated proton therapy (IMPT) demonstrates superior non-target tissue sparing with the use of IMPT. Retrospectively, we aim to investigate the dosimetric advantage of IMPT in regards to improved treatment tolerance in an elderly cohort.

We analyzed outcomes for patients receiving curative-intent radiotherapy, age 65 years and older. Outcomes included patient-reported outcomes (PRO) of side effects and physician-reported toxicities. Patients must have completed at least a baseline and one post-treatment assessment. PRO and physician-reported toxicities comparing IMPT and IMRT were analyzed using the Wilcoxan Rank Sum Test.

Of 126 patients, 48 patients met inclusion criteria. 98% had HPV/p16-positive cancers of the tonsil or base of tongue. 48% were treated with adjuvant radiotherapy, while 52% were treated with definitive-intent radiotherapy. 56% received IMRT while 44% received IMPT.

At the end of RT, patients treated with IMPT reported nonsignificant smaller decrements in dry mouth ($p=0.12$), sense of smell/taste ($p=0.11$), and feeling ill ($p=0.28$). At further follow-up, patients treated with IMPT were using less pain meds and have less swallowing dysfunction, dry mouth, problems with opening mouth, and troubles with social eating.

Physician-reported toxicities showed less severe nausea, oral pain, mucositis, and sore throat with the use of IMPT. At further follow-up, physicians reported less dysphagia, pharyngeal edema, mucositis, sore throat, and oral pain in the IMPT cohort.

For older patients, IMPT demonstrated trends for improvement in multiple acute head and neck symptom domains from both a patient and physician perspective.

PTC58-0159

DAHANCA 35 - proton versus photon radiotherapy for pharynx and larynx cancer: A randomized trial using a model based enriched population

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Background: Head and neck cancer patients suffer from serious side effects during and after radiotherapy - side effects that may be reduced with proton therapy. Models, developed in photon radiotherapy, describe the correlation between dose, volume and risk of side effects. DAHANCA, the Danish Head and Neck Cancer Group, has agreed upon that uncertainties concerning dose delivery, RBE and patient selection, justifies a randomization of patients.

Materials and Method: A comparative photon and proton dose plan will be made for all pharynx and larynx cancer patients, except patients with cancer of the nasopharynx and early glottic cancer. If the dose distribution of the proton plan indicates a clinically relevant reduced risk of observer-assessed dysphagia and/ or patients reported xerostomia, using the presently available best models, the patient is offered randomization to either proton or photon radiotherapy (2:1). Objective assessment of swallowing and salivary flow, acute and late toxicity, quality of life, socioeconomic endpoints and locoregional control are other important secondary endpoints.

Results: Inclusion for a feasibility trial is expected to begin in early 2019, and the randomized trial to begin during second half of 2019

Conclusion: National consensus has been reached to perform a complex randomized study with high demands for the decentralized abilities to create comparative dose plans and to refer patients to a national proton center. If the study reaches its goals, groundbreaking evidence will be created to guide the selection of patients for the optimal therapy in the future.

PTC58-0264

Pencil beam scanning proton radiotherapy in the treatment of nasopharyngeal cancer

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Introduction: Patients with nasopharyngeal cancer are candidates for proton radiotherapy due to large and comprehensive target volumes and necessity of sparing healthy tissues.

Material and methods: Between Jan 2013 to Jun 2018 we treated 40 patients with nasopharyngeal cancer (NPC) with IMPT (proton radiotherapy with modulated intensity). Median of age was 47 years, majority of pts. had locally advanced tumors (stage 2 – 8 pts. (20%); stage 3 – 18 pts. (45%); stage 4A – 10 pts. (25%); stage 4B – 4 pts. (10%). Median of total dose was 74 GyE (70-78 GyE) in 37 fractions (35–39). Bilateral neck irradiation was used in all cases. Concomitant chemotherapy was applied in 34 pts. (85%). Median follow up time is 24 months.

Results: Two-years OS, DFS and LC are 80%, 75% and 84%, respectively. Acute toxicity was generally mild despite large target volumes and application of concurrent chemotherapy, with skin toxicity and dysphagia as most frequent acute side effects. PEG was necessary in 4 pts. (10%). Serious late toxicity (G >3, RTOG) was observed in 1 pt. (2,5%) (dysphagia in patient with pre-existing disease of collagenous tissue).

Conclusion: IMPT for nasopharyngeal cancer patients is feasible with mild acute toxicity. Treatment outcome is promising despite the high percentage of very advanced disease in this group.

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PTC58-0183

Evaluation of robustness of posterior-beam-weighted proton treatment planning for oropharyngeal cancer

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Patients undergoing concurrent chemoradiation therapy (CCRT) for oropharyngeal cancer (OPC) frequently experience tumor regression or weight loss during treatment, which can result in dose delivery degradation such as critical increase on dose to organ-at-risk (OAR) and decrease on dose to target volume. This may require the patient repeat CT simulation to assess the dose change, and then estimate the necessity of adaptive re-planning. When it comes to making decision whether re-planning is required, the robustness of treatment plan against these anatomical change [PS1] must be considered, because it mitigates risks of dosimetric change on target volume as far as robustness ensures, eventually reducing labor-intensive efforts for re-planning. In this study, we present proton treatment planning of OPC which maximize robustness by varying beam weighting in the same beam configuration, observing dosimetric change on OAR we concern. Basically, two beams were used for OPC proton planning which are anterior-oblique (AO) beam and posterior-anterior (PA) beam, and three plans were made varying beam weighting ratio, AO/PA from 1, 2 to 3. Robustness of each plan was evaluated using four synthetic CT in which weight loss is simulated as contracting body contour partially by 2.5, 5, 7.5 and 10 mm. Dose change on OARs such as parotid gland, skin, brainstem and spinal cord were also analyzed. As a result, as weighting ratio increases, dosimetric change on target volume showed less and decrease of average dose decrease on parotid gland was shown, whereas dose on brainstem and spinal cord were increased.

PTC58-0446

Dosimetric comparison of adjuvant pencil beam scanning protons and intensity modulated radiation therapy following transoral robotic surgery for oropharyngeal cancers

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Purpose: Post-transoral robotic surgery (TORS) patients have increased swallowing difficulties with adjuvant therapies. For HPV+ oropharyngeal cancer (OPC**)** patients receiving adjuvant radiotherapy following TORS, pencil beam scanning (PBS) was compared to IMRT for target coverage and dose to organs at risk (OAR).

Methods: Eight consecutive patients were included. Contours were completed by one radiation oncologist. Plans achieved D95 and D99 to the CTV for proton with robustness evaluation for position and range and PTV for IMRT, respectively, while meeting institutional OAR constraints. Prescribed doses included: 60GyRBE (primary site), 54GyRBE, 60GyRBE and 66GyRBE (low-, intermediate- and high-risk disease to bilateral neck). Proton plans utilized 3-4 beams and multi-field optimization. Statistical analysis was performed using the paired-t test.

Results: Compared to IMRT, PBS plans resulted in statistically significant improved D95 ($p=0.001$) for intermediate risk CTV, lower mean dose to mean total constrictors (49.6Gy vs 36.0GyRBE; $p=0.008$), mean total larynx (42.0Gy vs 25.0GyRBE; $p=0.008$), mean oral cavity (33.6Gy vs 19.5GyRBE; $p=0.0002$), mean ipsilateral parotid (45.6Gy vs 33.7GyRBE; $p=0.008$), mean contralateral parotid (27.2Gy vs 20.0GyRBE; $p=0.008$), mean ipsilateral submandibular gland (64.3Gy vs 57.8GyRBE; $p=0.03$) and maximum spinal cord (42.5Gy vs 32.3GyRBE; $p=0.02$). There were no statistically significant differences between groups for maximum brainstem, mandible, V45 esophagus or mean contralateral submandibular gland.

Conclusions: There was significant dose reduction to several OARs with PBS vs. IMRT, especially for swallowing structures. Correlating reduction in doses to functional outcomes and cost-effectiveness may be helpful in guiding clinicians to the choice of radiation modality in the post-TORS setting.

PTC58-0727

Re-irradiation for recurrent scalp angiosarcoma: Dosimetric advantage of proton therapy over VMAT and electron therapy

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Background: Re-irradiation in the scalp area can be challenging given proximity to the organs at risk (OAR) like the eye and underlying brain. Our aim is to evaluate the dosimetric differences of volumetric modulated arc therapy (VMAT) and electron beam therapy (EBT) in comparison to 3-D proton beam therapy (PBT).

Methods: We evaluate a case of recurrent angiosarcoma of left temporal scalp status post prior tomotherapy overlapping treatments to 60 Gy in 30 fractions. VMAT, EBT and PBT plans were generated using Pinnacle. Both VMAT and EBT plans used a skin bolus versus no bolus used for the proton plan. Doses to the OAR's including cochlea, eyes, lens, lacrimal glands, optic nerves, optic chiasm, pituitary gland and underlying brain were compared.

Results: Re-irradiation treatment dose was 60 GyRBE. Representative comparison of the plan images is shown (Figure 1). Target volume coverage was comparable in all plans. Compared to VMAT and EBT, PBT plan showed significant reductions in mean and max doses to all OAR's (Table 1). Without the use of protons several OARs would have exceeded dose tolerance utilizing VMAT or electrons. Dose reduction of up to 100% was achieved for central and contralateral OAR's.

Conclusions: PBT as compared to VMAT and EBT resulted in meaningful dose reductions to all OAR's, while maintaining excellent target coverage. PBT shows a significant advantage in treating superficially located skin cancers like angiosarcoma without need for a bolus. PBT could be considered in the upfront treatment and certainly in the re-irradiation setting.

PTC58-0141

Acute toxicity profile in head and neck cancer patients treated with re-irradiation using proton therapy versus intensity modulated radiotherapy

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Objective: Proton therapy (IMPT) may represent a superior option compared to photon therapy (IMRT) for preserving the balance between treatment-related toxicities and local control for curative head-and-neck re-irradiation (re-RT).

Materials & Methods: We conducted a retrospective analysis of prospectively collected toxicity data for head-and-neck cancer (HNC) patients treated with re-RT using IMPT and IMRT. All patients had at least one prior curative radiation course to the head-and-neck region. Acute toxicity within 3-months of re-RT was recorded using CTCAE version 4.3. Statistical analysis was performed using Fisher Exact and Wilcoxon rank sum tests.

Results: Our cohort included 31 HNC patients treated with re-RT between April 2013 and December 2018 using IMPT (n=14) and IMRT (n=17). Median follow-up was 11 months. 77% (n=24) received definitive intent re-RT, while 23% (n=7) received adjuvant re-RT. Median re-RT dose was 66Gy whereas median total dose was 130Gy. IMPT used conventional fractionation and stereotactic-body-radiotherapy (SBRT) in 7 patients each (50%). IMRT used hyperfractionation in 76% (n=13) and conventional in 18% (n=3) and one SBRT. IMPT had lower rate of grade-3 acute toxicity for any given outcome when compared to IMRT (36% vs 71%, p=0.05), this effect was also seen in conventional IMPT compared to IMRT hyperfractionation (43% vs 69%), although statistically not significant (p=0.25). Toxicities assessed included dysphagia (7.1% vs 41.2%, p=0.03), mucositis (14.3% vs 35.3%, p=0.01), and dermatitis (14.3% vs 29.4%, p=0.02).

Conclusions: IMPT reduced rates of grade $\geq$3 toxicity in HNC re-irradiation compared to IMRT, despite differences in fractionation schedules. These encouraging results warrant further exploration through larger prospective studies.

PTC58-0136

18F-fluoromisonidazole (18F-FMISO) PET guided dose escalation with proton therapy in nasopharyngeal carcinoma (NPC): A feasibility and planning study

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Background: Tumor hypoxia is associated with resistance to radiation and increased rate of local recurrence. Selective dose escalation to hypoxic areas within tumor improve tumor control with acceptable side effects. The purpose of this study was to evaluate from a planning point of view the feasibility of dose painting with proton therapy to hypoxic area identified on 18F-FMISO PET-CT in NPC.

Methods: Nine patients participated in this planning study. Two proton plans were generated for each patient. The initial phase was planned with single-field uniform dose (SFUD) optimization using 2 fields to 10Gy in 2fractions to hypoxic volume identified on 18F-FMISO PET. The second phase was planned with intensity modulated proton therapy (IMPT) with robust optimization to deliver 70Gy to gross tumor volume with simultaneous integrated boost to a dose of 60Gy and 54Gy in 33fractions to high risk clinical target volume (CTV) and low risk CTV respectively. A plan sum was generated for assessment.

Results: Eight patients had identifiable hypoxic volumes on pre-treatment 18F-FMISO PET. The average hypoxic volume was 1.92ml(range:0.97-4.19ml). All plans met predetermined target coverage. The average D95 of hypoxic volume was 80.7Gy (SD:0.23Gy). The average Dmean of right and left parotid glands, brainstem, and chiasm were 22.2Gy, 26.2Gy, 49.3Gy and 16.80Gy respectively. The D1cc of temporal lobes of less than 75Gy was achievable in all but one patient.

Conclusion: Hypoxia-targeted dose painting is feasible with proton therapy without substantial dose increase to normal tissues above tolerance. Clinical trials are warranted to determine the clinical outcomes.

PTC58-0070

Clinical risk of carcinogenesis from passively scattered proton beams

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Background: Neutron contamination from high Z materials in a passively scattered beam has been cause for concern regarding carcinogenesis because neutrons are quite potent in this regard. Based on a combination of neutron dose measurements and theoretical calculations this risk has been shown to be as low or even lower than for photon irradiation techniques. However, to evaluate the true risk to patients, long term clinical outcomes need to be analyzed.

Methods: We studied a cohort of 322 patients, the vast majority treated for benign conditions, for the occurrence of in field and out of field secondary malignancies (SMs). Of the 322 patients, 164 were female and 158 were male. Ages ranged from 2–85 years, with a median of 40 years. 13% were <20 years, 27% were <30 years, and 69% were <50 years of age at the time of treatment. Their follow up ranged from 25 to 276 months, with a median of 150 months. The 41 patients under the age of 20 had a median follow-up of 15 years.

Results: A variety of 7 out of field SMs developed during the follow-up period, in keeping with observed rates in the general population based on the national cancer statistics. 8 patients developed intracranial meningiomas, but no in-field secondary malignancies were seen.

Conclusions: For out of field SM's no increased risk of developing a malignancy was observed. No SMs were observed in children and young adults.

Clinics: Eye / Breast / Pelvis Poster Discussion Sessions
PTC58-0091

Microdosimetric study and RBE measurement at CATANA proton therapy facility for the treatment of ocular melanoma

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CATANA (Centro di AdroTerapia ed Applicazioni Nucleari Avanzate) was the first Italian proton therapy facility dedicated to the treatment of ocular neoplastic pathologies. Since 2002, it's in operation at the LNS-INFN to date 400 patients have been successfully treated. Nowadays, a slightly increased biological effectiveness is considered in clinical proton treatment planning by assuming a fixed RBE of 1.1 for the whole radiation field. However, data emerging from various studies suggest and highlight how variations in RBE, which are currently neglected, might actually result in deposition of significant doses in healthy organs. Accurate knowledge of the RBE increase in eye proton therapy is of extreme importance as the distal part of the SOBP often involves critical anatomical regions like optic nerve and the macula for which an excess of biological dose could lead to patient's vision loss. A collaboration, between INFN-LNS, CMRP UoW, INFN-NA, IBFM-CNR, INFN-LNL, INFN-MI and INFN-TIFPA was established to perform an experimental measurement of major microdosimetric parameter the dose average lineal energy $y_d$to derive RBE value along a typical SOBP for eye proton therapy. Microdosimetry measurements along the SOBP were carried out using silicon-based detector microdosimeter,mini-TEPC and TEPC followed by application of MKM for RBE_{10}calculation. In this study, melanoma cells (MP38) and normal retina (ARPE19) cells were irradiated in a phantom along the same CATANA 62-MeV SOBP for RBE evaluation. Monte Carlo modeling of the same experimental set up using the Geant4 toolkit has been done. The simulated y_d were used as the physical input to MKM for RBE_{10}simulations. RBE derived from three mentioned approaches were compared.

PTC58-0609

Tumor volume definition for ocular proton therapy through advanced MRI imaging

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Purpose: Treatment planning for ocular tumors is typically based on a simplified eyeball and tumor (TV_{EP}) model scaled to match with the patient's fundus photography, ultrasound imaging and geometrical references provided by surgically implanted tantalum clips. Here we compare this approach with modelling of the eye and tumor delineation based on MR imaging.

Methods: MRI based volumetric ocular biometry was performed on 31 patients. All relevant ocular structures, such as the eye globe, lens, tumor (TV_{MR}) and clips, were manually segmented, and merged into a MR-based eye model. After alignment based on tantalum clips, this model was geometrically compared to the conventional eye model. In addition, the dosimetric consequences of adopting different models were evaluated by applying treatment plans optimised on TV_{EP} to TV_{MR} and vice versa.

Results: The two models show high geometrical similarity as regards the eye globe with median volume ratios of 0.98 (IQR:0.12) and Dice similarity coefficients (DSC) of 0.92 (IQR: 0.03). In contrast, TV_{MR} was on average half the size of TV_{EP} (volume ratio: 0.50, IQR:0.32) with a DSC of 0.62 (IQR:0.21). Dosimetrically, complete target coverage (V95=100%) was measured in 84% of cases when applying the TV_{EP} plan to the $TV_{MR,}$ with coverage not being achieved for ratios of TV_{MR}/TV_{EP} $>$0.95. Conversely, for plans optimized on TV_{MR}, only 16% demonstrated acceptable coverage of TV_{EP}.

Conclusions: Although MRI remains the most viable solution to replace clip-based identification of intraocular lesions, further developments on MR sequence and, possibly, the integration of ancillary imaging modalities are required.

PTC58-0615

A novel deep-learning framework applies to analysis the image characteristics of uveal melanoma tissue in MRI

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Purpose: To evaluate an automated segmentation pipeline of uveal melanoma (UM) in magnetic resonance imaging using a novel deep-learning technique.

Material and Method: The dataset is composed of 28 healthy adult eyes and 28 UM patients. MR acquisitions are performed with a 1.5T Siemens scanner with the resolution of 0.5x0.5x0.5mm^3 for T1-weighted (T1w) and 0.5x0.5x0.5 or 0.82x0.82x0.8mm^3 for T2-weighted (T2w). Our method can be summarized in five major steps (see Fig.1: Image analysis proposed framework). First, the pre-processing input data for noise reduction and intensity normalization. Second, the prior shape information extraction of the sclera and lens. Third, the 2D attention map extraction based on a CNN-base classification. Fourth, the tumor and retinal detachment differentiation based on a second CNN-base architecture (Unet) and Gabor textural separation. Finally, a set of image features will be estimated for each object segmented including first-order statistics, shape and textural features.

Results: We evaluate the accuracy of the tumor segmentation by using the Dice coefficient: 83.4$\pm$4.5% for T1W and 82.7$\pm$5.1% for T2W. Figure 2a&b (Result of tumor and retinal detachment extraction) shows the example of retinal detachment and tumor differentiation in 1 patient.

Conclusions: Our method allows the quantitative image analysis of UM and retinal detachment for the integration of 3D information into the UM proton therapy treatment.

PTC58-0623

Fluorescence-based verification of the proton beam's position during the irradiation of intraocular tumors

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The proton therapy of intraocular tumors is usually performed at a horizontal beam line. The patient is looking at a fixation light to insure the optimal irradiation position for the eye. The eye position is verified prior to irradiation by orthogonal X-ray imaging. During the irradiation the anterior part of the eye is observed by a video camera. For on-line verification of radiation field position and eye movements, a novel method based on proton-induced luminescence in blood vessels of the ocular fundus is being tested.

The proton-induced luminescence is measured in a phantom with a blood vessel structure of a typical ocular fundus, which can be filled with fluorescein ($c = 1.0$ g / l). Therefore, the phantom is positioned in water at 18 mm water depth and irradiated with a spread out Bragg peak. The proton-induced luminescence is detected with a CCD camera.

The position of the irradiation field can be detected with an accuracy of 0.13 mm for applied doses between 8.4 Gy and 23 Gy. The accuracy depends on the location and number of irradiated vessels. A position change of the model in the order of 0.2 mm during the irradiation was be detected within 4 s.

The proton-induced luminescence on the dye fluorescein allows in vivo verification of the irradiation field and eye movement during proton irradiation. Further experiments with more complex cases and optimized imaging are being conducted to demonstrate a clinical implementation.

PTC58-0135

The cost-effectiveness of proton therapy hypofractionation for regional nodal irradiation in non-metastatic breast cancer

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Introduction: Regional nodal irradiation (RNI) for early stage breast cancer (ESBC) patients yields improved clinical outcomes but increases mean heart dose (MHD), which correlates with cardiovascular events. Proton therapy reduces MHD, but its cost may be prohibitive. Hypofractionation (HF) may resolve cost barriers. Cost-effectiveness analyses provide insight into the potential value of proton vs photon HF-RNI and may inform trial design for their comparison.

Materials and Methods: A Markov cohort simulation model was designed to explore the cost-effectiveness of proton vs photon HF-RNI from the payer perspective in 16 fractions for patients with non-metastatic breast cancer (NMBC), assuming similar outcomes to conventional RNI (C-RNI). In the base case, patients age 50 entered the model after RT and could develop local or distant recurrence, coronary heart disease (CHD), or death. Framingham risk calculator informed CHD risk, which was modified by the MHD. Subgroup analyses based on primary laterality, relapse risk, and age were performed. A willingness-to-pay threshold of $100,000/QALY was used.

Results: Proton RNI was not cost-effective in the base case nor in women with right-sided cancers. It was cost-effective ($67,490/QALY) for women with left-sided cancers, particularly in left-ESBC (Stages I-II) ($60,664/QALY). Figure 1 demonstrates the relationship between 20-year breast cancer recurrence risk and cost-acceptability. Left-ESBC was cost-effective from the societal perspective.

Conclusion: HF-RNI is not currently the standard of care but is under active investigation. If HF-RNI proves to yield equivalent outcomes to C-RNI, this analysis suggests HF-RNI with proton therapy would be cost-effective and supports its further investigation.

PTC58-0412

Proton radiotherapy for left-sided breast cancer in patients with pectus excavatum anatomy

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Purpose: For breast cancer patients with challenging anatomy, it can be impossible to cover the entire breast and IMN without exceeding dose limits to the organs at risk (OAR) using photon therapy. Proton therapy may present a solution.

Methods and Materials: Five patients with left-sided breast cancer, and pectus excavatum, were included. Three treatment techniques were compared (Eclipse TPS vs13.7): Standard two-field tangential photons, VMAT with two arcs (separate isocenters), and IMPT 2-3 fields (see figure 1). Plan objective was PTV (breast+IMN) 95-107% (50Gy), dose limits to whole heart (V40Gy<5%, V20Gy<10%), left anterior descending coronary artery (LAD, V20Gy=0%, V10Gy<5%) and lung (V20Gy<25%, mean dose<18Gy).

Results: Target coverage was best and most consistent in proton plans – see figure 2a. Target dose could not be achieved with photons, however for proton plans V90%>99% could be achieved for all patients.

For proton plans, doses to OAR were below limits for all patients. For whole heart, mean[range] V40Gy was 1.2[0;5.6] for protons, 1.2[0.2;3.1] for VMAT and 9.2[0.8;16.7] for tangential plans. The mean[range] V20Gy was 1.7[0.7;2.3], 13.6[8.4;27.4] and 16.4[4.2;28.2] for protons, VMAT and tangential plans. Mean heart dose was 1.6[0.9;3.1]Gy, 11.4[7.5;15.1]Gy and 9.2[3.6;14.4]. Doses to LAD are shown in see figure 2b.

For lung, mean[range] V20Gy was 15.6[14.3;17.7] for protons, 30.9[25.8;39.4] for VMAT and 34.7[24.3.51] for tangential plans. The mean[range] mean lung dose was 7.6[7;9.6]Gy, 17.2[15.6;21]Gy and 17.3[12.3;24.4]Gy.

Conclusion: For patients with left sided breast cancer and pectus excavatum, proton therapy could achieve adequate target coverage without compromising doses to OAR for all patients.

PTC58-0469

Proton partial breast irradiation preferentially spares the heart and lungs over modern whole breast radiotherapy

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Purpose: To compare target coverage and normal tissue sparing of state-of-the-art photon whole breast irradiation (WBI) and proton partial breast irradiation (PPBI).

Methods: Consecutive women with node negative breast cancer treated with lumpectomy and adjuvant WBI, without regional nodal irradiation, or PPBI were included. WBI was delivered with 3-dimensional conformal tangential fields, targeting the breast CTV with a 5 mm expansion to PTV to a median dose of 40 Gy in 15 fractions. Left-sided WBI patients were treated in deep-inspiratory breath hold. PPBI was delivered with a median of 2 multi-field optimized beams, targeting the lumpectomy cavity plus 1 cm, to a median dose of 21.9 Gy in 3 daily fractions. Setup uncertainty analyses of +/- 3 mm isocenter shifts in each translational axis and 3% beam range uncertainty were performed to ensure robust target coverage and normal tissue sparing. Dosimetric parameters, collected prospectively, are primarily presented as % prescription and we excluded the boost component of WBI for uniformity of plan comparisons.

Results: 836 women were treated between 2015-2018; 762 received WBI (274 [36%] with boost to the lumpectomy cavity), and 74 with PPBI. Patients treated with PPBI were older and had more favorable breast cancer (Table 1). Patients treated with PPBI had comparable target coverage but significantly lower heart and lung doses (Table 2).

Conclusions: PPBI reduces exposure to the heart and lungs. Follow-up is needed to determine if these dosimetric advantages translate into improved clinical outcomes.

PTC58-0502

Bone marrow suppression during postoperative radiation for bladder cancer and comparative benefit of proton therapy: Phase-II trial secondary analysis

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Introduction: For patients with high-risk bladder cancer (pT3+ or N+), locoregional failure remains a challenge after chemotherapy and cystectomy. An ongoing prospective phase-II trial (NCT01954173) is examining the role of postoperative photon radiotherapy for high-risk patients using volumetric modulated arc therapy (VMAT). Proton beam therapy (PBT) may be beneficial in this setting to reduce hematologic toxicity. We evaluated for dosimetric relationships with pelvic bone marrow (PBM) and changes in hematologic counts before and after pelvic radiotherapy and explored the potential of PBT treatment plans to achieve reductions in PBM dose.

Methods: Eighteen (18) enrolled patients (median age 70) were retrospectively analyzed following pelvic radiation per protocol with 50.4-55.8 Gy in 28-31 fractions. Comparative PBT plans were generated using pencil-beam scanning and a 3-beam multi-field optimization technique (Figure).

Results: There was a decrease in mean nadir values compared to pre-radiation values for white blood cells (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC) (all $p<0.001$), and platelets ($p=0.03$). Increased mean PBM dose was associated with nadirs in WBC (Pearson CC 0.593, $p=0.015$), ANC (CC 0.597, $p=0.024$) and hemoglobin (CC 0.506, $p=0.046$), while the PBM V5-V20 was correlated with platelets (Table). Comparative proton therapy plans decreased the mean PBM dose from 26.5 Gy to 16.1 Gy ($p<0.001$) and had significant reductions in the volume of PBM receiving doses from 5-40 Gy.

Conclusion: Increased mean PBM dose was associated with decreased hematologic nadirs. PBT plans reduced PBM dose and may be a valuable strategy to reduce the risk of hematologic toxicity in these patients.

PTC58-0286

Organ sparing potential and intra-fraction robustness of IMPT for cervical cancer

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Introduction:

Chemoradiation (CHRT) for cervical cancer results in severe chronic bowel toxicity and acute hematologic toxicity often causing CHRT discontinuation. IMPT may reduce OAR dose, however inter- and intrafraction variability may affect target coverage. While interfraction variability can be addressed by adaptive replanning strategies, robustness against intrafraction variability should be maintained.

Purpose: To report on the potential of IMPT to reduce OAR dose and to study target coverage robustness of IMPT compared to VMAT versus intrafraction motion.

Materials and Methods: Pre-fraction and post-fraction repeated CTs (reCTs) from 5 cervical cancer patients were available, for whom target volumes included the para-aortic region. Two-field IMPT (2F), four-field IMPT (4F) and two-arc VMAT primary treatment plans were created. Each reCT was contoured and registered to the planCT. Subsequently, all 3 plans were recomputed and target coverage robustness against isocenter shifts and range uncertainty was evaluated on each reCT. Nominal OAR doses and the worst case post-pre intrafraction dose differences delivered to 98% of the GTV and CTV (GTV + uterus + vagina) vs intrafraction bladder volume differences were analyzed.

Results: Mean whole bowel dose was reduced by nearly a half (Figure 1A) and all OAR doses were significantly lower (Table 1) for both IMPT plan types compared to VMAT. IMPT showed similar target coverage robustness as VMAT against all intrafraction bladder volume changes (Figure 1B).

Conclusion: Robustly optimized IMPT treatment plans for cervical cancer patients show equivalent robustness against intra-fraction variability when compared to VMAT treatment plans, but offer significantly better OAR sparing.

Clinics: CNS / Pediatrics / Lung Poster Discussion Sessions

PTC58-0156

An analysis of vertebral body growth on pediatric cancer patients after proton radiotherapy

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Purpose: To predict body growth, we analyzed the relationship between the vertebral body (VB) growth and the irradiation dose of the proton therapy (PT) in children.

Methods: Between 2009 and 2017, 21 pediatric patients who received PT to the VB were selected in this study. These patients included 9 males and 12 females, and had a median age of 4 years (range 2-10). The tumor was as follows; neuroblastoma 11, Wilms' tumor 3, Ewing's sarcoma 2, ependymoma 2, Hairy cell astrocytoma 1, Nasopharyngeal carcinoma 1 and Renal cell sarcoma 1. The VB height was measured with CT or MRI before and about 1 year after PT, and the growth rate (% per year) in each VB height was calculated. The irradiation dose for each VB was evaluated with dose distribution. Measurable non-irradiated VBs were also evaluated as control.

Result: Median observation period was 13.7 month (9.4 – 19.1). 312 vertebral bodies were evaluated (182 were irradiated, 130 were non-irradiated). Of 312, 50 were cervical, 187 were thoracic and 75 were lumber spine, respectively. Median PT dose was 30.6 Gy (RBE) (range 10.8 - 56.8). Analyzing all VBs, negative correlation between the PT dose and the growth rate was significantly observed ($p = 0.001$). Median growth rates were 8.0% and 3.3% at non-irradiated and irradiated VBs.

Conclusion: Significant correlation between the growth rate of the VB height and PT dose was estimated. Using this approach, we can establish a method to predict the body height in each pediatric cancer patients.

PTC58-0585

Shape and texture analysis of skull-base chordomas to predict the outcome of pencil beam scanning proton therapy

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Purpose: Skull-base chordomas (sbC) are rare bone tumors presenting within the clivus or spinal axis, characterized by significant tissue heterogeneity. Their shapes are variable, likely determined by proximity to surrounding anatomic barriers, making them a typical indication for proton therapy (PT). Here we investigate whether shape and/or textural features of the pre-treatment tumor correlate with clinical outcome.

Methods: We retrospectively analyzed 50 sbC patients treated using PBS-PT at our institute. Pre-PT tumor shape and texture (Tab.1) were evaluated on DWI- and T2w-MRI images using in-house developed software and were classified using clustering algorithms (Kmeans) considering both tumor and organs-at-risk (OARs) features, which were cross-correlated with recurrences.

Results: Fig,1 shows two contrasting tumors. (a) is a case with high sphericity and small surface-area (0,86 and 2409mm^2) which did not recur. In contrast the tumor in (b), with values of 0,27 and 8846mm^2 respectively, did recur. Overall, clustering analysis uniquely identified 4 out of 5 recurrences based on these morphological features. However, due to the small number of recurrences, this result is not statistically significant. Other features, such as compactness and signature-mean were significantly correlated (correlation-coeff.$>$0.85; Fig.1c) but no correlation was observed between textural features and clinical outcome.

Conclusion: Sphericity and surface-area have been found to be potential predictive factors for treatment outcome in sbC. Greater surface values and protrusions (e.g. Fig.1b) could indicate a larger area of contact between tumor and normal-tissue, thus increasing the probability of tumor infiltration. We are currently extending our analysis to a larger patient cohort.

PTC58-0389

Radiation-induced brain injury in meningioma patients treated with proton or photon therapy

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Purpose: It is unclear whether rates of brain injury are different with proton therapy due to uncertainties in end of range effects. This study compares rates of brain injury after proton or photon therapy.

Materials and Methods: We retrospectively reviewed 38 patients treated with proton therapy and 39 treated with photons. Re-irradiation patients were excluded. Radiation induced brain injuries were categorized into white matter lesions (WML) defined as newly detected abnormal T2 signal intensities, or radiation necrosis (RN) defined as newly detected abnormal T2 and T1 post contrast signal intensities. Imaging was reviewed by an experienced neuro-radiologist and radiation oncologist. Toxicity was graded as per CTCAE v4.03.

Results: Median follow-up time was 18 mo for proton and 24 mo for photon therapy. There was no significant difference between the groups for WHO grade, radiation dose, history of diabetes, or history of stroke. The cumulative incidence of WML at 2 years was 38.3% after proton and 45.0% after photons ($p=0.60$). The cumulative incidence of RN at 2 years was 17.9% after proton and 4.2% after photons ($p=0.01$). With protons, grade ≥ 2 was recorded in 7 patients and one patient had a grade 4/5 event. With photons, grade ≥ 2 was recorded in 3 patients and one patient had a G4/5 event.

Conclusion: Patients treated with radiation have high rates of developing T2 signal intensity abnormalities. However, in our series, patients were more likely to develop parenchymal T1 post contrast abnormalities after proton therapy. Additional studies are required to confirm these findings.

PTC58-0296

Active spot-scanning proton therapy for intracranial meningiomas: CNAO experience

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Objective: Proton therapy (PT) is an alternative therapeutic option for unresectable meningiomas, mostly located in the skull-base, and a complementary treatment for complex and irregular tumors located in close proximity of critical organs at risk (OAR) as optic-pathways and brainstem where only subtotal or partial resection is possible. Aim of the study was to evaluate treatment results and toxicity in patients (pts) with meningiomas treated with active spot-scanning PT

Methods: 79 pts with intracranial meningioma (histologically proven 50/79) were treated with PT between October 2012 to December 2017. Pts, tumor and treatment characteristics were summarized in Tab1. 59 pts had skull-base lesions. 44 pts were treated as primary treatment (exclusively PT=32 pts, postoperative PT=12 pts), 35 pts were treated for recurrence after surgery. 29 pts had radiological diagnosis (28/29 skull-base lesions) and in all these cases ^{68}Ga-DOTATOC-PET was performed before treatment. The total dose was 55.8 Gy (RBE). GTV ranged from 2.3-205.71 cm$^{3.}$ Toxicity was assessed according to CTCAE- V4.03 scale.

Results: median follow-up was 17 months. No high-grade (grade 3-4) treatment-related toxicity was observed. Local control was 99%. Only one patient, affected by atypical meningioma, had local recurrence 22 months after the end of the treatment. Two pts with atypical and anaplastic meningioma respectively had "out-of-field" recurrence 20 and 8 months after the end of the treatment.

Conclusions: PT is a safe and effective treatment for pts with intracranial meningiomas, and it allows to deliver high local doses even in complex anatomy (as skull-base lesions) while sparing critical OARs

PTC58-0368

Proton beam therapy for meningioma: Treatment outcome and toxicity

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Purpose: Proton beam therapy (PT) is of increasing interest especially in tumors in close proximity of critical structures like skull base meningioma. Treatment outcome and toxicity data collected in a prospective registry of a single institution are presented.

Methods: Between July 2013 and May 2018, 55 adult patients with meningioma with a median age of 55.7 y (20.1-79.6 y) were treated and were prospectively enrolled in the in-house registry ProReg. The cohort consisted of 15 male and 40 female patients. Histopathology included WHO °I (36, 65.5%) and WHO °II (8, 14.5%). Eleven patients (20%) received no biopsy. Twenty-two (40%) patients received definitive PT. Adjuvant PT was administered after gross total resection and subtotal resection in 8 (14.5%) and 25 (45.5%), respectively. The median total dose of PT was 54Gy (54-60Gy) applied in 27 (27–33) fractions.

Results: The median follow-up time from the primary diagnose was 3 years (0.4 – 26.1 y) and after the end of PT 1 year (0-4.5 y). Local disease control was achieved in 52 patients (94.5%). Local recurrence occurred in 1 patient and 2 patients had local progress after treatment. All patients were alive at last follow-up. PT was well-tolerated. No new higher-grade (CTCAE $\geq$°3) acute toxicity occurred. Long-term follow-up after PT showed 1 new CTCAE °3 toxicity as increasing vision deficit due to tumor progression.

Conclusion: Current data support good early tumor control and feasibility of PT in meningioma. However, further follow-up data is required to assess long-term outcome.

PTC58-0662

Proton therapy for craniospinal radiochemotherapy (chemo-CSI) reduces myelotoxicity and improves chemotherapy completion in adult medulloblastoma (aMB)

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Purpose: Combined radiochemotherapy for aMB improves survival versus radiation alone but is highly toxic. Proton therapy for chemo-CSI spares vertebral marrow, potentially reducing myelotoxicity and improving rates of chemotherapy completion. This analysis tracks myelotoxicity and chemotherapy completion rates in aMB patients treated with proton chemo-CSI, comparing them to NOA-07 trial results for photon chemo-CSI.

Methods: Patients age$\geq$15 were included if they received vertebrae-sparing proton chemo-CSI for newly-diagnosed aMB and were planned to receive concomitant-phase vincristine during radiotherapy followed by $\geq$4 cycles of adjuvant chemotherapy. Craniospinal axis was treated to 23.4 or 36 CGE with subsequent boost to 54-55.8 CGE. Myelotoxicity and chemotherapy completion were evaluated using NOA-07 criteria. Correlations with toxicities were conducted using chi-square analysis; survival estimated using Kaplan-Meier method.

Results: Twenty-four (24) patients at a single institution met inclusion criteria. Median follow-up was 2.4 years. Median age was 28 (range: 18-58), 46% were female, 54% average-risk, and 50% received 23.4 CGE CSI. 2-year PFS and OS were 88% and 100%, respectively. Of 21 patients with available hematologic data: 95% received cisplatin, 76% vincristine, 67% CCNU, and 62% cyclophosphamide. 86% and 80% completed $\geq$4 and $\geq$6 cycles of adjuvant chemotherapy, respectively, versus 70% and 63% in NOA-07. Adjuvant-phase cyclophosphamide use correlated with grade$\geq$3 leukopenia ($p<0.01$) and neutropenia ($p=0.01$). Table 1 displays myelotoxicity results.

Conclusions: Proton chemo-CSI for aMB increases rates of adjuvant chemotherapy completion, reduces rates of concomitant-phase leukopenia and, excluding patients receiving cyclophosphamide, lowers rates of adjuvant-phase myelotoxicity compared to photon chemo-CSI control (NOA-07, which omitted cyclophosphamide).

PTC58-0675

A Proton Collaborative Group(PCG) Phase I Study of hypofractionated proton therapy for stage II-III non-small cell lung cancer

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Background: We investigated whether proton therapy would allow for safe dose intensification with concurrent chemotherapy for patients with stage II/III non-small cell lung cancer (NSCLC).

Methods: Eighteen patients from four different Proton Collaborative Group institutions were enrolled and treated on an IRB-approved prospective phase I study. Patients received concurrent chemotherapy with hypofractionated proton therapy to a planned total dose of 60 Gy(RBE), but with increasing dose per fraction in a 5x5 step-wise fashion. Arm 1 delivered 2.5 Gy/fraction (n=5); arm 2 delivered 3 Gy/fraction (n=5); arm 3 delivered 3.53 Gy/fraction (n=7); and arm 4 delivered 4 Gy/fraction (n=1). Dose arms were considered safe provided 0 of 5 or 1 of 7 patients developed a radiation-related serious adverse events (SAEs) within 90 days of starting treatment. Patients received consolidative chemotherapy or immunotherapy after completing concurrent therapy per institutional policies.

Results: No radiation-related SAEs occurred within the first 90 days on arm 1 or 2. One patient developed an SAE on arm 3; however, no further SAEs occurred on arm 3 after 7 patients were enrolled. One patient received treatment on arm 4 and did not develop an SAE.

Conclusions: Hypofractionated proton therapy with concurrent chemotherapy to a dose of 60 Gy(RBE) in 2.5-3.53 Gy/fraction is well-tolerated. A phase II study of hypofractionated proton therapy with concurrent chemotherapy for patients with stage II/III NSCLC is warranted.

PTC58-0434

Patient engagement in the design of a randomised trial of proton beam radiotherapy versus photon radiotherapy for good prognosis glioma

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Introduction: UK Neuro-Oncologists and multidisciplinary colleagues are developing one of the first randomised clinical trials of proton beam radiotherapy (PBT) to compare quality of life (QOL), cognitive function and other late effects in adults with good prognosis glioma following either PBT or photon radiotherapy. The feasibility of running randomised studies with PBT is an important consideration, particularly in respect of participants' views of a randomised design requiring treatment at national centers. We sought patient and carer engagement on our proposals to ensure we incorporate their views.

Methods: To explore these issues, we invited patients who had previously completed radiotherapy for oligodendroglioma and their carers to attend a focus group in Manchester in November 2018. Fifteen participants attended. We sought views on our trial proposal through small group discussions centerd around 5 questions, led and facilitated by neuro-oncologists, a research radiographer,neuro-psychologist and statistician.

Results: Participants strongly endorsed the trial proposal and positively highlighted the opportunity to access PBT within a clinical trial and the group recognised and supported the need for randomisation and stated this should be 1:1. Patients disliked some traditional terminology such as 'trial' and 'neurocognitive tests' and preferred 'research study' and 'neurocognitive assessments'. Patient and carers expressed the need for careful consideration of issues around travel and accommodation during PBT away from home. Interestingly, participants considered that standard QOL questionnaires fail to address some important areas reflecting daily wellbeing.

Conclusion: We acknowledge and will now incorporate these important patient and carer observations to strengthen our study and add validity to the key study endpoints.

PTC58-0344

Preliminary results of pencil beam scanning proton and carbon ion therapy for skull base and cervical spine chordoma and chondrosarcoma

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Purpose: to evaluate the short-term tumor control and toxicity of skull base and cervical spine chordoma and chondrosarcoma in patients treated with pencil beam scanning proton and heavy ion therapy.

Methods: Between May 2014 and December 2017, a total of 84 patients have been treated with proton and/or carbon ion RT in shanghai proton and heavy ion center. There was 47 male and 37 female patients. The median age was 37 years (range, 14-70 years). 41(48.8%) patients were treated for primary tumors, whereas 43(51.2%) had recurrent tumors after surgery and/or radiotherapy. Thirteen (15.5%) of all the patients received radiotherapy previously. The median gross tumor volume was 36.5cc (range: 1.6-232cc).

Results: Eight patients received proton therapy, 28 patients received combined proton and carbon ion therapy, 48 patients received carbon ion therapy. The median follow-up period was 24 months (range, 3-91 months). For the entire cohort, the 2-year local control, progression free and overall survival rate was 88.2%, 78.5%, and 86.3% respectively. On multivariate analyses, more than 50cc GTV volume (0.033) was the significant factor for predicting PFS, while re-irradiation ($p=0.003$) was the only significant factor for predicting OS. The acute toxicity was mild with on grade 3-4 effects. Late toxicities of unilateral temporal lobe changes in 2 patients.

Conclusions: The short-term outcome of particle therapy for chordoma and chondrosarcoma was favorable. Larger tumor volume and re-irradiation was related to inferior survival. Further follow-up is needed for long-term efficacy and safety.

PTC58-0248

Scanning beam proton therapy versus photon IMRT for stage III lung cancer: Comparison of dosimetry, toxicity and outcomes

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Purpose: There is limited clinical data on scanning-beam proton therapy (SPT) in treating locally-advanced lung cancer, as most published literature is with passive-scatter technology. There is increasing interest in whether the dosimetric advantages of SPT compared with photon therapy can translate into superior clinical outcomes. We present our experience of SPT and photon intensity-modulated radiation therapy (IMRT) with real-life dosimetry, and outcomes in patients with stage III non-small cell lung cancer (NSCLC).

Methods: Patients with stage III NSCLC treated at our center between 2013-May 2018 were identified in compliance with an IRB-approved study (64 patients=34 SPT+30 IMRT). Most proton patients were treated with pencil-beam-scanning (28/34), 6/34 with uniform-scanning. Fisher's exact test, Chi-square test, and Mann-Whitney test were used to compare groups. All tests were two-sided.

Results: Patient characteristics are in Table 1. Mean dose to lung, heart, and esophagus were lower in the SPT group, with most benefit in the low dose region (Table 2). Esophagitis and dermatitis grades were not different between the two groups (Table 2). Grade 2+ pneumonitis rate was 21% in the SPT group and 40% in the IMRT group (p=0.1). Overall survival and progression free-survival were not different between SPT and IMRT.

Conclusions: We report our experience with scanning beam proton therapy and photon IMRT in stage III NSCLC, showing lower dose to normal organs (lungs, heart, esophagus) with SPT than IMRT. There is no statistically significant difference in toxicity rates or survival, although there may be a trend towards lower rates of pneumonitis.

General: New Horizons

PTC58-0621

Proton beam diagnostics for ultra-high dose rate irradiations

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In the context of the novel *FLASH radiotherapy* mode, irradiations at ultra-high dose rates are increasingly becoming of interest. To ensure controlled and correct dose application in this yet largely unexplored dose application regime, adaptations in beam diagnostics are necessary and several possible options are already published for experimental electron Linacs [1, 2] as well as a proton machine [3]. We present a successfully tested and currently in use solution for our ProBeam spot scanning proton therapy system, which enables small animal irradiations in only a fraction of a second with doses of 25 Gy and higher and a dose reproducibility within <2%. [1] E. Schueler et al., Int J Rad Onc 97, 1, 195-203 (2017). [2] M. Jaccard et al., Medical Physics 45, 2, 863-874 (2017). [3] A. Patriarca et al., Int J Rad Onc 102, 3, 619-626 (2018).

PTC58-0301

Online beam and range monitoring in a static toroidal gantry delivery configuration

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GaToroid is a novel fixed toroidal gantry, based on superconducting magnets, able to deliver the dose at discrete number of angles without rotation of the magnets or the patient. In order to become a feasible option for particle therapy delivery, it requires the integration of beam and range monitoring functionality.

We propose to implement the beam monitoring through high timing resolution pixelated silicon detectors that will match the beam delivery windows foreseen by the GaToroid design. Moreover, we plan to exploit the azimuthal gaps between the beam entrance windows by installing PET detectors that will provide high–precision online range monitoring.

In terms of performance, the fully integrated delivery and monitoring system would allow:

- highly flexible and fast beam delivery, with a static gantry much lighter and smaller than the existing ones, subjected to no restrictions on beam timing, beam energy or positioning precision associated to its movement;
- beam monitoring with single particle counting capability for fast measurement of beam fluence and position;
- online range monitoring by means of a 3D measurement of the beam-induced activity distribution and of the prompt gamma emission profile, with the goal of an overall range precision of about 1mm obtained within 1 minute of the treatment delivery start.

Preliminary results of the system design simulations and of the expected performance will be presented.

PTC58-0128

Plan for new multi-modality therapy in Daejeon, Republic of Korea

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Recently South Korea has had two hadron therapy centers under construction: The Korea Institute of Radiological & Medical Sciences in Gijang and Yonsei University Hospital in Seoul. In addition, South Korea already has two proton centers: The National Cancer Center and Samsung Proton Center. However, there is still lack of particle therapy facilities compared to the number of cancer patients. Interest in hadron therapy is increasing, yet all centers are focused on clinical therapy, not intensive research. In general, the number of patients that require treatment with proton therapy is higher than carbon therapy; still, the requirement for both ions are solid. For this reason, the city of Daejeon, located in the center of South Korea, is planning a new multi-modality therapy center associated with the Korea Advanced Institute of Science and Technology. This center is aiming to treat patients with both protons and carbon ions associated with basic research. The Daejeon multi-modality therapy center will not only help covering the lack of proton therapy center but also provide effect of carbon ion treatments. Daejeon's multi-modality therapy center will also invest intensively in research, such as new hadron therapy technology, medical imaging associated and knowledge transfer.

PTC58-0527

Survey on variations of knowledge and perception amongst radiation oncologists across India regarding proton beam therapy (PBT)

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Background: This survey aims to provide an insight into the variations of knowledge and perception amongst radiation oncologists across India regarding proton beam therapy (PBT).

Methods: Participants of this anonymized online survey included radiation oncologists from all over India. Unique links were electronically mailed from a database populated from professional associations. Descriptive statistical analysis was applied to closed-ended questions, expressed as frequency for categorical variables. Chi-square test and Fisher's exact test was used for comparisons.

Results: Total number of respondents were 253.Seventy percent respondents said 1-10% patients from their current practice were eligible for PBT. Modern PBT significantly different from older proton techniques as believed by 74% respondents. Although 50% respondents believed PBT is suitable for only small sized tumors; chordomas, chondrosarcomas, other skull base tumors (94%) followed by pediatric tumors (90%) were the top indications for PBT. Dose-escalation possibility was believed to be amongst the top PBT benefits by 82% respondents in adults. Limited access (67%), lack of high-quality evidence (61%) for PBT are responsible for slower adoption of PBT across the world, while in India it is lack of awareness amongst the practitioners (46%) and public (30%). Conducting randomized controlled trials (PBT vs photon) for children was deemed ethical by 69% respondents. Need for more awareness about PBT was expressed by 90% respondents.

Conclusion: In view of the wide variation in perception and knowledge amongst the radiation oncologists across India, our survey provides significant information which can act as a suitable benchmark to create awareness regarding PBT.

PTC58-0235

ELIMED/ELIMAIA: The first Users beamline dedicated to irradiation studies with laser-driven ion beams

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The main direction proposed by the community in the field of laser-driven ion acceleration is to improve particle beam features in order to demonstrate reliable approaches to be used for multidisciplinary applications.

The mission of the laser-driven ion target area at ELI-Beamlines (Extreme Light Infrastructure) in Czech Republic, called ELI Multidisciplinary Applications of laser-Ion Acceleration (ELIMAIA), is to provide stable, fully characterized and tuneable beams of particles accelerated by Petawatt-class lasers and to offer them to the user community for multidisciplinary applications. The focusing, selecting, measuring and irradiating parts of ELIMAIA, constitutes the so-called ELIMED (ELI MEDical and multidisciplinary applications) portion.

At ELIMED, very high-dose-rate (not less than 10^5 Gy/min) controlled proton and ion beams, with energy ranging from 5 to 250 MeV, will be transported up to the in-air section where absolute dosimetry will be carried out. A transmission, dual-gap air ionisation chamber will provide the on-line measure of the dose at the irradiation point. The maximum expected error in the final dose released to the sample is expected to be within 5%. ELIMED first irradiation is scheduled for 2020 when the first radiobiological campaign for in-vitro cells irradiation with controlled fast beams is expected.

In this work, the status of the ELIMED/ELIMAIA beamline will be reported along with a complete description of the main dosimetric systems and of the first preliminary calibrations. The expected final beam characteristics, in terms of dose per pulse, dose-rate, beam spot size, directly derived by Monte Carlo simulations, will be reported, as well.

PTC58-0311

Proton grid therapy: Dosimetric characterization of planar slit collimators

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Introduction: The narrow beams used in proton grid therapy can be produced with collimators. In this study we have carried out a dosimetric characterization of single-slit collimators of different slit widths (SW). We compared experimental results obtained at a pencil-beam scanning beam line with results obtained from Monte Carlo (MC) simulations.

Method: Single-slit brass-alloy collimators (SW = 1, 2, 3 mm) were mounted on the nozzle snout. Transversal dose profiles were measured for monoenergetic 100 MeV beams with the Lynx detector at three depths (z = 4, 24, 76 mm) in a solid water phantom. A beam model of the Skandion Clinic (Uppsala) beam line was implemented in the TOPAS simulation software. Three collimator–phantom distances (CPDs) of 0, 60 and 285 mm were used in the simulations to study the importance of this variable for the dose distributions produced.

Results: The Lynx measured values and the MC simulation results are in close agreement which indicates that the beam model used in the simulations produces realistic results (Figure 1). The CPD influences the measured field size, and the dose distribution produced by collimator scatter to a large extent (Figure 2).

Conclusions: The collimator should be placed as close to the irradiated object as possible to reduce the dose produced in between the narrow beams at the entrance surface. The beam model used in this work can be used for further studies related to multi–slit collimation of proton beams.

PTC58-0061

New 3D-microdetectors for microdosimetry in proton minibeam

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The development of new solid-state devices has opened the experimental verification of the hadron therapy beam LET distribution even at nominal fluence rates. This new instrumentation can be used to commission the clinical beams and also to assess the Relative Biological Effectiveness (RBE). Likewise, proton minibeam radiation therapy (pMBRT) is a novel concept that combines the benefits of proton therapy with a remarkable normal tissue preservation when irradiated with submillimetric spatially fractionated beams. This promising technique has already been implemented at a clinical center (Institut Curie-Proton therapy center of Orsay, ICPO) by means of a first prototype of a multi-slit collimator. The goal of this work is to study the performance of a new set of 3D-microdetectors for microdosimetry measurements in the heterogenous dose deposition produced by pMBRT.

The new 3D-microdetectors used are a type of silicon diode with a 3D-cylindrical electrode etching with an inner volume that matches a sensitive volume similar to a subcellular structure. The complete ICPO beamline and pMBRT irradiations setup as well as 3D-microdetectors were modelled using GATEv7.0 simulations. A clinically relevant energy (100 MeV) was used. For minibeam generation the brass multi-slits collimator used in the experiments was modelled. The proton beam average energy was modulated with an in-house wedge system formed by two equal 10° angle wedges made of Lucite.

Preliminary results show that this new device is useful to microdosimetry characterization at nominal clinical fluence rate. Ongoing microdosimetry measurements are being performed at ICPO

PTC58-0604

A medical ethics ranking system for allocation of scarce proton therapy resources

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Introduction: A single-room proton facility operates at full capacity of 16 hours daily. A triage system was developed to optimally allocate this scarce resource for maximal patient benefit. Prostate patients were excluded as only limited spots were allocated to them.

Methods: In cooperation with members of the clinical ethics and Hem/Onc, a multi-domain scoring system was created to help allocate available proton starts to patients with greatest clinical benefit. Patients were prospectively peer-reviewed during proton rounds in a multidisciplinary manner. In order to look at the feasibility, this was applied to new proton starts and they were evaluated according to the highest composite score based on anticipated clinical benefit (1-6pts), expected survival duration (0-8pts), strength of evidence (1-2pts), KPS (0to-2pts), and enrolled in research protocol (1-3pts).

Results: Fifty-one patients (43adult and 8pediatric) were evaluated from September through December 2018 while machine was at capacity. Median and mean composite scores for all patients were 11 and 11.55 respectively (range4-21,SD4.42). Median and mean scores was 20 and 19.25 respectively for pediatrics (range16-21,SD1.48). Median and mean scores for adults were both 10 and 10.12 respectively (range4-17,SD3.07). All pediatric and adult patients with high scores started treatment in a timely fashion. Approximately two potential proton patients per month were diverted to other modalities due to low scores and unavailable proton starts, not including those denied by their insurer.

Conclusion: This system would enable patients with strong levels of clinical benefit, evidence, and expected survival to initiate treatment more expeditiously than those for whom proton benefits are less clear.

PTC58-0028

IMRT for breast and lymph node irradiation: A comparative dosimetric study between tomotherapy, VMAT and proton therapy

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Purpose: To compare all treatment options available in our institution in terms of volume coverage and organs at risk (OAR) sparing.

Material and Methods: We studied 10 patients treated for breast cancer (BC) with lymph node (LN) involvement. Prescription dose was 63 Gy to the tumor bed, 51.8 Gy to the whole breast and 50.4 Gy to the LN in 28 fractions. Helical Tomotherapy (HT) with a field width of 2.5 cm (HT_FW_2.5) was the treatment used in these 10 cases. HT_FW_5, or Volumetric Modulated Arc Therapy VMAT and proton therapy with Pencil Beam Scanning (PT_PBS)plans were designed and compared to the clinically approved plan (HT_FW_2.5) using dosimetric indices for OAR (D_{max} for the spinal cord, D_{mean} for the heart, both lungs and contralateral breast) and PTV ($D_{95\%}$, $D_{2\%}$ and Homogeneity Index). A paired Student's t-test ($\alpha=0.05$) was used to cross-check all plans.

Results: Results reported in Table 1 show that PT_PBS plans show that an excellent PTV coverage can be maintained along with significantly lower doses to the heart, contralateral lung and contralateral breast.

Conclusions: Our results showed that PT_PBS treatment should be considered in the near future as it showed great potential benefit to lower the risk of side effects. Prospective studies are needed to evaluate the clinical impact of this treatment.

PTC58-0627

Investigation on FLASH therapy using a high frequency linac for protons

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Background and Significance: Recent *in-vivo* studies demonstrated that electrons delivered at high dose rates within 0.5 s (FLASH) to cancerous tissues inhibit tumor growth as well as with conventional therapy, but significantly sparing surrounding healthy tissues.

Specific Aim: In this study, we investigated the possibility of using proton pencil beam scanning (PBS) for uniform FLASH irradiations using a pulsed proton linac and considered the beam parameters needed to achieve FLASH dose rates.

Methods: A commercial treatment planning system (RaySearch Labs AB, Stockholm; model RayStation; version 6.99R) was used to perform treatment plan calculations to deliver 10 to 40 Gy uniform doses to 2 cm^2 targets at various depths. Parameters from a commercial proton linac (Advanced Oncotherapy plc, London; model LIGHT) were considered to deliver the needed doses within the 0.5 s FLASH time limit at a pulse rate of 200 Hz. High dose rate requires a high number of protons per pulse; therefore, in our study, we consider 200 to 800 Mp (mega proton) per pulse, assuming 1 pulse per spot.

Results and Conclusions: Our analytical study shows that LIGHT could deliver high doses within 0.5 s with dose rates of the order of 40 Gy/s and the same time structure of 3 GHz conventional electron linacs. Optimized parameters such as spot spacing, weight and size can aid in decreasing the delivery time to produce the FLASH effect with protons using a clinical machine setting. The LIGHT Solution and its successive evolutions are subject to conformity assessment and market authorization.

PTC58-0306

Beamline optimization studies for small animal irradiation at clinical proton therapy facilities

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Interest in proton therapy is rapidly emerging. However, the biological effects of protons interacting with human tissue are not completely understood. Preclinical studies may play a major role in tackling those questions. Proton beamlines tuned for clinical use usually do not provide beam properties required for small animal irradiation. Building or adapting a beamline exclusively for such studies can be costly and unpractical. The project SIRMIO aims at developing a small-animal irradiation platform for deployment in standard proton therapy centers. A beamline study based on Monte Carlo simulations and input from experimental data was conducted to obtain proton beams with energies ranging from 20 up to 75 MeV using a set of magnets allowing for tunable spot sizes down to less than 1 mm FWHM. Several arrangements of doublets, triplets and quadruplets of either permanent or electromagnets were studied, coupled with passive elements such as degraders and collimators to yield suitable conditions for proton energy, spot size and shape, and beam emittance. Dose homogeneity and dose delivery times for typical small-animal irradiation were assessed using simulation and planning data. Using the case of a 30 MeV proton beam as an example, the results showed that entrance-to-peak and plateau-to-peak ratios of ∼40% and ∼52%, respectively, can be achieved. When compared to other beamline designs consisting of passive elements only, fluence of secondary neutrons was reduced to ∼10%. Supported by ERC grant 72553.

PTC58-0445

The LARA Radiobiology Facility for the Center for the Clinical Application of Particles

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The Center for the Clinical Application of Particles (CCAP) is an interdisciplinary collaboration to develop the technologies, systems, techniques and capabilities necessary to deliver a paradigm shift in the clinical exploitation of particles. The CCAP aims to deliver a broad program of measurement of the radiobiological effect of particle beams and systematic studies of radiobiological mechanisms using a laser-driven ion source. The design of the Laser Accelerator for Radiobiological Applications (LARA) facility will be presented.

PTC58-0004

Flash radiotherapy: A look at ultra-high dose rate research and treatment plans

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Research is ongoing in the field of ultra-high dose rate radiation therapy. Early pre-clinical studies show normal tissue sparing while not compromising tumor control when the beam-on-time for the normal tissue is under one second.

These very exciting discoveries, however, require dose rates of 40Gy/sec - 120Gy/sec (or 240,000cGy/min - 720,000cGy/min). Proton therapy presents the most immediate opportunity for translation of Flash radiotherapy into human patients.

This talk will focus on covering most of the recent research findings to-date (high-level literature review with photos) and then follows with an overview of some of the treatment planning concepts which could be employed to make proton Flash treatments a reality for humans.

PTC58-0120

30MeV accelerator-based BNCT system and the current status of its clinical trials in Japan

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Since the 1950s, numerous global clinical attempts at boron neutron capture therapy (BNCT) utilizing research reactors have been made. An accelerator-based (AB) neutron source is imperative for future hospital use because regulations for reactors are too strict to install and operate in a hospital environment. Accordingly, considerable developmental efforts for AB neutron sources are being made around the world. In this presentation, the first commercial AB-BNCT system developed by Sumitomo, which is used for human treatments, is reported.

BNCT consists of two key components. The first is an epithermal neutron source and the second is a boron compound. The Sumitomo system employs a 30MeV proton cyclotron and a beryllium target as a neutron source. The neutron energy generated at the target reaches up to 28MeV and is then moderated down to epithermal range, the energies of which are appropriate for human irradiation.

In 2012, Sumitomo and Stella Pharma Corporation (Stella) started phase I clinical trials for brain tumor and head and neck cancer using a boron compound, boronophenylalanine (INN : borofalan(^{10}B)), provided by Stella, and the recruitment and irradiation of our phase II clinical trials completed in 2018.

A medical device application process is now under way for the first time in Japan and its regulatory status is also presented here.

PTC58-0499

PROBE: Proton Boosting Extension for imaging and therapy

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The ProBE project aims at accelerating protons from a particle therapy cyclotron to the c.330 MeV required for proton tomography of adults. To obtain the c. 50 MV/m gradients required to achieve 100 MeV gain in a suitably short distance, we propose the use of an S-band side-coupled standing-wave structure with novel properties. In this poster we discuss the progress from initial designs to the current prototype due to be tested at CERN. This linac may also be used to make linac-based proton therapy systems smaller than is presently possible.

PTC58-0352

Evaluation of a new experimental setup for radiobiology experiments at the E1 area of the ELI-NP building using FLUKA

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Currently there are two state-of-art research infrastructures in Romania, ELI-NP and CETAL, which use ultrahigh power lasers (10 PW in the first case, 1 PW in the second) for a wide array of research activities. One of the declared purposes of the ELI-NP project is to explore the possibility of developing new techniques in proton therapy by using laser-accelerated beams. However, it is highly probable that some of the initial experiments will be directed towards gaining more insight into the radiobiology of proton therapy and the factors that influence the relative biological effectiveness of the beam.

The present paper analyses the feasibility of such radiobiology experiments at the E1 area of the ELI-NP building, using proton beams with maximum energies of up to 500 MeV. The FLUKA code is used to simulate a case in which a proton beam with 40^0 divergence is collimated on a 10-cm-diameter exit window. The beam is used to irradiate a parallelepipedal water phantom placed in air at a distance of 10 cm from the window. The phantom has a 20x20 cm^2 cross area and a depth of 10 cm. We present the results regarding beam homogeneity and symmetry at the phantom entrance side, as well as the depth dose curves and the depth LET curves, both for primary protons and for all ionizing particles. We conclude by showing how this information can be used for designing the setup of radiobiology experiments at an ultrahigh power laser area.

PTC58-0476

Neutron capture enhanced particle therapy (NCEPT): An opportunistic dose amplification for particle therapy via capture of internally generated thermal neutrons

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Neutron Capture Enhanced Particle Therapy (NCEPT) is an enhancement to proton and heavy ion therapy being developed by the Australian Nuclear Science and Technology Organisation (ANSTO) and the University of Wollongong, Australia. NCEPT amplifies the impact of particle therapy by capturing thermal neutrons - a byproduct of treatment, produced in and around the target - inside cancer cells to deliver extra dose to the tumor. NCEPT uses drugs currently used or in development from the field of neutron capture therapy, which concentrate in cancer cells and are optimized for thermal neutron capture. NCEPT delivers the prescribed radiation dose to the tumor while exposing healthy tissue to less radiation compared to standard particle therapy. It also delivers significant dose to nearby satellite tumors too small to be visible to cancer imaging systems.

The feasibility of NCEPT is supported by Monte Carlo simulations evaluating thermal neutron fluence for a simple uniform treatment plan (Figure 1). In this work, we present the first in-vitro experimental results obtained with carbon and helium beams at HIMAC (National Institute for Quantum and Radiological Science, Japan) in July 2018. For primary ion doses of the order of 3 Gy delivered to cultured human glioblastoma cells (T98g) treated with clinically-feasible concentrations of 10B and 157Gd-based neutron capture agents, cell proliferation was reduced by approximately 80% compared to untreated controls.

Results obtained with the carbon beam are shown in Figure 2. These results provide strong experimental evidence supporting the proposed method and potential for improving treatment efficacy and reducing side-effects.

PTC58-0089

Determining the number of proton facilities required for optimal care

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Radiotherapy is currently used in 50% of cancer patients. Proton therapy (PT) allows more precise delivery of radiotherapy and can reduce the long-term damage to normal tissues surrounding a cancer. But it is expensive, costing two to ten times more than traditional radiotherapy, depending on the system.

Meaningful, large scale, randomized trials with protons versus photons are challenging and are likely to be inconclusive. Instead, the pre-treatment comparison of PT versus state-of-the-art Intensity Modulated Radiotherapy (IMRT) in individual patients using pre-set metrics of plan quality will be used to decide whether PT has any advantage. This assessment can now be made objectively by treatment planning software systems. Payers, government and insurers, will use set criteria to assess the value of PT in an individual using a comparative equation incorporating tumor control, early and late toxicity and overall lifetime costs of care. Such analyses will determine logically the level of the therapeutic plateau in the relationship of cost to gain in clinical outcome.

Here, we have carried out an extensive meta-analysis of published estimates for the optimal utilization of PT in radical radiotherapy. The range is wide from 1% to 40%. Recent policy studies from several European countries indicate a 10 -15% conversion to PT in patients treated with radical intent. Based on the world literature, one PT facility treating 500 new patients a year for a population of 4m seems a reasonable estimate for optimal cancer care.

PTC58-0253

Modelling to rapidly compare photon and proton dose distribution in individual patients

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Our aim is to produce a model that allows a comparison of images after treatment with different radiation modalities. This reduces the requirement for full clinical double planning and to plan only those patients that show evidence of likely benefit from protons after a quick, low-cost and semi-automated assessment process.

Our approach is to first produce a model showing the whole process outside the clinical environment. These results are not for any clinical purpose. This approach has allowed us to modularize the entire process. Some elements have slotted in applications that are fulfilling their function very well. While we still have some element of human input within the pathway, we continue to build scripts and functions to fulfil complete automated delivery. We now have a semi-automated end-to-end process that can feed in an image and produce a pdf report at the far end. At this stage, the quality and usability in a clinical environment was not an objective.

This approach has allowed us to run two parallel projects. One investigates what automation we can use to aid clinical workload and processes. The second examines ways of refining the model to fully automate this process using not only defined images but also DICOM-RT feeds. Automated treatment planning is rapidly evolving. We will demonstrate our double planning comparative model which effectively determines the normal tissue complication probability (NTCP) from both protons and photons rapidly and automatically from PTV and OAR outlines.

PTC58-0255

Disaster recovery planning for a proton therapy network

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We are building a global network of proton centers using single gantry systems in the UK and abroad. All are linked through a central server in London Docklands with appropriate backup. Most hospital and community radiation systems have on-site based IT solutions. We currently support these systems, but they can give rise to a number of critical issues in the event of local failure from whatever cause. We describe here our networked solution for IT providing LINAC and proton radiotherapy as well as chemotherapy. We will describe our strategy for:

- Disaster Recovery (DR) for complete loss of power, fire, flood or structural collapse
- Loss of radiation equipment from hardware failure or explosion
- Loss of cyclotron function
- Failure of local IT systems

Most hospital multiple unit LINACS are located on the same site, making them still vulnerable to disaster events. Single gantry proton systems have no substitution potential on the same site but networked IT allows immediate patient transfer to an operational site.

Moving the key applications to a secure central data center can serve many sites, which with a little adjustment in processes to enable each site to act as a backup and provide an emergency resource. With this IT concept, we provide a robust or viable DR plan that takes allows continuity of patient care in the event of a catastrophic failure at any single site.

PTC58-0324

Electron beam radiobiology up to 1 GeV and 50 Gy/sec at the Berkeley Lab Laser Accelerator (BELLA) Center

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Laser-generated ion beams can provide much higher doses and dose-rates than conventional ion sources, and preclinical tests have demonstrated clinical advantages of ultra-high doses and dose rates in eradicating tumors. The Lawrence Berkeley National Laboratory is working with the University of California, San Francisco to develop an experimental platform for investigating radiobiological effects of laser-accelerated electron and ion beams for the treatment of cancer.

Preliminary published data indicate an advantageous differential response between tumor and normal tissues at ultrahigh dose rates with sparing of normal tissue. We are investigating the mechanisms underlying this differential response, and are comparing effects to BELLA-accelerated electron reference beams.

We are focusing on radioresistant prostate tumors since they are hard to treat with conventional methods. We therefore selected three human prostate tumor cell lines, and one normal human prostate line. We are beginning with *in vitro* studies, but plan future studies with tumor cells implanted in mice.

We will present preliminary data comparing survival for two different endpoints (colony-forming ability and MTT) after exposure to 300kVp X-rays, and to low-energy (∼10MeV) versus high-energy (1GeV) electrons, over a dose range of 1-10 Gy, and a dose-rate range of from 1 Gy/min up to 50 Gy/sec. We anticipate that high repetition rate petawatt laser plasma accelerator performance will allow future tailoring of electron and particle energy and numbers to specific applications in the field of cancer cell biology for research users of the BELLA Center. Supported by LBNL Laboratory-Directed Research and Development funding under Contract No. DE-AC02-05CH11231.

PTC58-0086

Energy sweep compact rapid cycling hadron therapy (ESCORT)

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A novel concept of hadron therapy allowing tracking irradiation on a moving and deformed tumor target has been proposed (Ken Takayama, "ESCORT", presented at New Technologies in Hadron Therapy Workshop, IEEE NSS-MIC 2018). The concept is characterized as follows;

1. Its beam driver is a fast cycling induction synchrotron (20 Hz), where a fully stripped heavy ion beam is delivered from the laser ablation ion source, the injected ion beam is captured in the barrier bucket and accelerated with the induction step voltage, a beam spill is continuously extracted by the energy sweep extraction method combining the programed barrier bucket leak and the lattice characteristics with the localized large momentum dispersion function (Leo K.W *et al.*, *Phys. Rev. Accel. & Beam* 19, 042802, 2016).
2. A combination of beam profile monitors and the full-body Liq. Xe 3*g* camera is used to obtain the dose profile/position in depth by detecting prompt *g*s. The accompanied X-ray camera also catches the position/profile of the tumor target. Signals are quickly processed in computers and the irradiation errors are found at 20 Hz.
3. The errors signals are transferred to the switching power supply energizing the induction cells to adjust the extraction timing. The position error signals are feedbacked to the fast deflecting magnet, which is excited with a different current every cycle so as to realign the scanning beam spot on the desired position.

PTC58-0155

Governance and procurement process for proton beam therapy (PBT) equipment in the new National Cancer Center Singapore (NCCS) building

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Purpose: To describe the governance and procurement process for Proton Beam Therapy (PBT) equipment in new National Cancer Center Singapore (NCCS) building.

Methods: Approval to establish a proton beam therapy facility in the new NCCS building at Outram Campus was obtained in 2012. A Board-level committee was formed to provide governance over the procurement process. Under this board, the project committee was formed to manage the procurement process. A two-stage procurement process was adopted. A Request-For-Information (RFI) was first called. Potential Proton Beam Therapy Equipment Vendors (PTEVs) provided base information about their equipment and their company strengths and profiles. Shortlisted PTEVs were invited to participate in the second-stage Request-For-Proposal (RFP) wherein detailed proposals were submitted. Proposals submitted by shortlisted PTEVs were evaluated by 7 separate evaluation teams namely: Technical, Service, Interface (Building), Contract mark-up, Organization, Commercial, and Price. To ensure that the merits of the proposals by PTEVs were not influenced by price, a two-envelope system process was employed within the RFP exercise. The price proposal was not evaluated until the 6 other teams had completed their assessment based on technical/functional of the vendors' proposals. Down-selected PTEVs were invited to improve their offers in a Best-and-Final-Offer (BAFO) exercise.

Results: A PTEV was selected to be the Preferred PTEV. A second PTEV was selected to be the Reserve PTEV.

Conclusion: The procurement process for PBT equipment in the new NCCS has been conducted in a transparent and open manner as described above.

PTC58-0158

Method to prevent accidental X-ray exposure to straying patients and staff during in-room imaging at National Cancer Center Singapore

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Purpose: To ensure safety in proton therapy processes and prevent accidental X-Ray exposure to straying patient and/or staff from entering the treatment room during in-room imaging in the new Proton Therapy Center at National Cancer Center Singapore whilst maintaining safety, show, and efficiency.

Methods: The new NCCS Proton Therapy Center will have in-room imaging capability for each of its four full rotating gantries. In-room imaging enables therapists to image the patient without needing to walk out of the treatment room, thereby increasing efficiency. As part of safety treatment doors will be left opened during patient setup and imaging as they are interlocked with the PBT equipment. No proton beam can be delivered whilst the doors are kept open. However, leaving the doors open runs the risk of patients and staff straying into the room during imaging, thereby exposing them to unnecessary x-rays.

Results: A digital Area Status Display (ASD) along with retractable crowd barrier will be strategically placed in the maze to deter and warn patients and staff from straying into the room. Treatment doors can remain open to ensure safety of therapists in the room and maximize workflow efficiency. Aesthetic interior design will not be compromised.

Conclusion: The method to be employed in the new Proton Therapy Center at the new NCCS building would allow NCCS to maintain safety for its staff and patients, and promote efficiency in the overall treatment process.

PTC58-0223

Proton quality assurance through the Global Harmonisation Group

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The Global Harmonisation Group for Quality Assurance in Clinical Trials (GHG) has established a subcommittee for proton quality assurance. The goal of the subcommittee is to combine particle therapy and QA expertise from around the world for the purpose of harmonizing clinical trial credentialing (including dosimetry audits) of particle therapy centers.

The subcommittee consists of members from the European Organisation for Research and Treatment of Cancer (EORTC), the US Imagining and Radiation Oncology Core (IROC), the Japan Clinical Oncology Group (JCOG), the UK Radiotherapy Trials Quality Assurance Group (RTTQA), the Trans-Tasman Radiation Oncology Group (TROG), the International Atomic Energy Agency (IAEA), and the Australian Clinical Dosimetry Service (ACDS).

The subcommittee members have shared details of their existing proton QA programs to review where there are gaps in services and room for growth and collaboration. Three working groups have been established to focus on specific components of proton therapy review: (1) Dosimetry/Equipment QA, (2) Treatment Plan Assessment, and (3) Patient Positioning, Immobilization, IGRT and Treatment Review. Dosimetry and Equipment QA have been developed by individual QA groups and the GHG are comparing the various methods to ensure equivalence. We are collaborating on the development of anthropomorphic phantoms, funded through JCOG. The working group on Treatment Plan assessment is developing consensus guidelines for case review of proton plans.

The standardization of such practices will enable global collaboration for proton clinical trial research, helping to boost the statistical power of clinical trials.

PTC58-0102

The High-Current Sumitomo Superconducting Isochronous Cyclotron (sc230) for proton therapy

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Sumitomo Heavy Industries, Ltd. is newly developing a superconducting isochronous cyclotron (SC230) for a new proton therapy system which is low cost, compact and ultra-high current beam. The beam energy, the maximum beam current, and the isochronous magnetic field of the new cyclotron are 230 MeV, 1000 nA, and 4 T respectively. The ultra-high beam enables to deliver the high dose to the whole volume of a moving target within one breath-hold by means of fast line scanning method.

A superconducting magnet is composed of two NbTi coils and yoke. NbTi coils are conduction-cooled by four 4 K Gifford-McMahon cryocoolers without liquid helium. The yoke weight is about 65 tons and diameter is 2.8 m, which is the smallest AVF cyclotron for this purpose. Inside the cyclotron, two RF cavities are in deep valleys. Another two valleys are used for beam monitoring and vacuum pumping. Extraction elements are one electrostatic deflector, two passive magnetic channels. Around the beam extraction radius, eight harmonic coils are equipped for a precessional extraction method. By adopting the precessional extraction method, simulated extraction efficiency is more than 70 %.

The superconducting magnet has been manufactured and confirmed to generate 4 T in 2018. We are currently measuring a magnetic field distribution and manufacturing other components of the cyclotron. The beam test will be performed in 2019.

Overview of the development plan and status will be presented.

PTC58-0153

Particle therapy in Singapore: Planning for a national proton beam therapy (PBT) facility

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Purpose: Singapore's cancer prevalence is expected to triple by the year 2030, in line with an aging population. The National Cancer Center Singapore treats 62% of the national cancer load. Expansionary plans for a new comprehensive cancer center presented the best opportunity to study the feasibility of a multi-gantry PBT facility in the new building.

Methods: Planning began in 2008. An estimated fifteen percent of patients who require radiotherapy will benefit from proton therapy. Initial case-mix was based on the Swedish estimates. Guidelines from the NHS, ASTRO and various countries were used to estimate the patient load for PBT. Modelling of throughput capacity was performed using the Manchester and various models for a multi-gantry room proton center. Based on these, a 4-gantry PBT system was proposed, for a steady-state treatment capacity of between 800-1000 patients a year, treating within 1.5 to 2 shifts. Ramp-up strategies of 3 to 7 years to steady-state were studied. A fixed-beam room was also planned for research.

Results: Government approval for the PBT facility was given in 2012. The new center will be operational in 2020-21 with 8 LINACs, with the PBT facility starting a year later with 2 gantries. Fully operational, the new center will also have 17 LINAC bunkers and 2 brachytherapy suites.

Conclusion: There are several levels of governance within the healthcare cluster and the Ministry of Health Singapore, which is the government body regulating the utility of PBT in Singapore. Clinical indications as well as healthcare financing for PBT will also be regulated.

PTC58-0562

Breast cancer proton beam therapy and proton CT on a rotating platform instead of a gantry

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At our proton therapy center, a large fraction of patients will be either treated on or waiting for availability of the gantry. As we possess only one room that houses a gantry, this leads to a practical bottleneck. We are exploring high-quality, cost effective alternative treatment techniques to decompress the clinical load on our single gantry.

Based on our prior clinical experience with treatment in a standing or seated position on a rotating platform at the Fermilab Neutron Therapy Facility, we wanted to explore the feasibility of this concept at our proton center. Specifically, we aimed to estimate the potential of this alternative as a means of reducing the number of breast cancer patients treated with our gantry. We gathered data on breast cancer patients treated on the gantry from June-August 2018 and determined the proportion of cases that required a "couch kick". Of all breast cancer cases treated in this time interval, only 16% required a couch kick at all; including primary plans and boosts, this figure fell to 8%.

Because the geometry of treatment with a gantry on an unkicked table is identical to treatment with a fixed horizontal beam and the patient in a standing or seated position on a rotatable platform, we conclude that up to 92% of breast cancer patients treated with the gantry at our facility could potentially be treated on a customized, low-cost, rotatable platform as an alternative. With such a platform, proton CT can become far more feasible than gantry-based methods.

PTC58-0579

Proton arc therapy improves plan quality in the presence of range and setup uncertainties compared to intensity modulated proton therapy

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Proton arc therapy (PAT) is likely to offer better dose to the targets and sparing of healthy tissue than intensity modulated proton therapy (IMPT) due to larger numbers of control points. This hypothesis comes from experience with conventional radiotherapy where volumetric arc therapy (VMAT) improves dose distributions and reduces sensitivity to uncertainties compared to fixed field intensity modulated radiotherapy (IMRT) in many cases. At the moment, PAT is not in clinical practice. Several groups compared PAT plans optimized with commercial treatment planning software to IMPT in nominal cases only and showed promising benefits.

Since proton therapy is sensitive to treatment uncertainties, this study aims to compare PAT to IMPT plans not only in the nominal cases but also as results of 2 kinds of treatment uncertainty (CT calibration and set up errors). We choose to work in 2 dimensions with an in-house Python optimizer as this reduces complexity, offers flexibility to explore novel optimization methods and gives results applicable in 3 dimensions. The cases chosen were a unilateral head & neck (H&N), a bilateral H&N and a skull base chordoma.

Table 1 shows the IMPT and PAT plan metrics for the unilateral H&N case as an example. The results indicate that PAT offers higher target conformality and homogeneity albeit at the cost of low dose levels to larger volumes of healthy tissue in nominal and uncertainty scenarios than IMPT. This suggests that PAT has the potential to improve dose distributions and reduce sensitivity to uncertainties compared to IMPT.

PTC58-0674

Proton ready: Easing the uncertainty with end to end testing

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As the first NHS service in the UK to deliver high-energy proton beam therapy (PBT) treatments to patients, it was of paramount importance to ensure time between commissioning and first treatment delivery was utilised effectively by the multi-disciplinary team (MDT; Physics, Radiographer and clinicians).

The UK care quality commission states that NHS services should be safe, caring, effective and well lead[1report]. This coupled with the requirement of the PBT service to report to NHS England and prove service readiness which met a large number of quality standards with a locally established competent, well informed and practiced team[2report]. A project plan was therefore devised to ensure that the proposed PBT patient pathway was fully tested and each stage in the pathway had associated procedural and quality documents.

Following from applications training, 8 patient pathways were identified and during a 5-week period between October and December 2018 the PBT processes were tested. Tested areas included (but not limited to):

- Referral to MDT meeting
- Paperless processes and scheduling
- PBT Treatment delivery, including imaging to establish routine workflow
- Quality management system documents
- Staff training
- Contingency / Machine breakdown processes
- End of treatment activities

End to end testing followed the Plan-Do-Check-Act cycle[3report] to track and test workflow and changes. The Christie will share our experience of the end to end testing process, to assist in planning and future development of new centers. Providing examples of how we utilised expertise of different specialist teams in each aspect of the process, to define workflow, share learning and decision making. 1) https://www.cqc.org.uk/sites/default/files/20180911_QI_hospitals_FINAL.pdf. 2) https://www.engage.england.nhs.uk/consultation/proton-beam-therapy-service/user_uploads/proton-beam-therapy-service-spec-proposition.pdf. 3) https://improvement.nhs.uk/documents/2142/plan-do-study-act.pdf.

PTC58-0516

Feasibility study to using Si detector for secondary radiation monitoring during proton therapy applications

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Nowadays, there is a rapid increase in the number of proton therapy centers worldwide due to proton has significant benefits over conventional photon therapy, delivering a large dose to the tumor and no dose to the healthy structures beyond. However, one of the concerns about proton therapy is the secondary radiation that is created during treatment. Secondary radiation created as a result of proton interactions within the human tissue depends on the target material, the beam energy and the delivering technique which in turn may increase the probability to develop secondary cancers in the surrounding tissues. Therefore, the aim of this research is to investigate, monitor and track the dose distribution of protons and associated secondary radiation, neutrons and gammas, when delivering the prescribed dose to the targeted cells.

In this project we using Geant4 simulation toolkit to simulate the proton beam and its interactions with a water phantom and silicon detectors in it. The water phantom contains two silicon pixel sensors fully submerged in the water and located in the main path of the proton beam in order to track the primary proton particles and measure the Bragg peak by means of the particle energy loss in the sensors. On the phantom edge there are two sandwich sensors which involves two planar silicon diodes separated with LiF film as a neutron converter layer to increase the thermal neutron capture probability to measure the secondary radiation in the form of neutrons generated in the water volume of the phantom.

PTC58-0411

Concomitant rectal spacer and endorectal balloon in proton beam therapy for localized prostate cancer

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Background: In prostate radiotherapy, rectal displacement with either rectal spacer or endorectal balloon (ERB) has been shown to reduce both treatment toxicity and intrafractional shifts. In proton beam therapy (PBT) there is also potential benefit from immobilizing the rectum and prostate relative to the pelvic bones though which the treatment beams pass. In our center, prostate cancer patients are implanted with the BioProtect biodegradable rectal spacer balloon prior to initial planning scans. A MEDRAD Pro-Tekt Endorectal balloon is also inserted at each scanning and treatment session. We aim to investigate the feasibility of and clinical and dosimetric advantage from concomitant rectal spacer and ERB in pencil-beam-scanning PBT for prostate cancer.

Methods and Results: The data for the first 10 prostate cancer patients has been analyzed.

CT, MRI, and daily cone beam CT images throughout the course of treatment and post treatment MRI scans were used to assess:

1. Intrafractional shifts by measuring the distance from the prostate to standard pelvic bone reference points
2. Changes in rectal volume
3. Distance and direction of travel of the anterior rectal wall
4. Bladder filling status
5. Bio-degrading of rectal spacer balloon

Dosimetric analyses of target and organs at risk (OARs) are also presented. Patient reported outcomes and side effects were assessed using the common terminology criteria for adverse events (CTCAE) and Radiation Therapy Oncology Group (RTOG) toxicity criteria during follow up.

General: New Horizons Poster Discussion Sessions

PTC58-0079

PBS plan correction for MR-guided proton therapy in the presence of in-line magnetic fields

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A novel technique combining magnetic resonance imaging (MRI) and proton therapy may allow fully exploiting the potential of high dose conformation in proton therapy (Raaymakers *et al* 2008). It should provide high soft tissue contrast imaging of patients during treatment, reducing geometrical uncertainties and related treatment margins. However, the magnetic field of the MRI scanner impacts the proton beam delivery (Oborn *et al* 2015). This contribution presents two strategies to modify the proton pencil beam scanning (PBS) plans to correct for the presence of an in-line magnetic field. The first strategy introduces changes within the dose calculation engine of the treatment planning system (TPS) to account for the effect of the magnetic field during plan optimization. The second strategy simply applies an energy-dependent rotation offset of beam spots during plan delivery. We considered fringe and imaging magnetic fields of 0.5, 1.0 and 1.5 T adapted from a realistic split bore MRI scanner. Plan delivery for a water phantom, liver tumor and prostate cancer were simulated with Monte Carlo simulations using TOPAS (Perl *et al* 2012). Results clearly indicate that modifications are required to deliver acceptable plans. The degradation of the plan quality depends on the field strength, tumor site, shape, and the field configuration. Plans with both modification strategies are equivalent to the reference plans without magnetic field. In summary, the workflow for proton PBS can be adapted for precise plan delivery in MR-guided proton therapy in the presence of in-line magnetic field.

PTC58-0553

FLASH proton dosimetry and achievable dose rates in a scanned proton beam for geometrical fields

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Purpose: Dose rates above a certain threshold (> 30Gy/s) could have a protective effect on healthy tissue – the FLASH effect – but may challenge standard dosimetry procedures when such fields are delivered and measured. In this work, we investigate the performance of ionization chambers when exposed to proton dose rates in the FLASH domain for pencil beam scanning (PBS).

Method: To determine what dose rates a modern commercial PBS treatment unit can achieve when pushed to its limits for simple geometrical fields, and to examine the dose rate response of the primary beam monitor (PBM), Faraday cup measurements have been employed. In addition, the dose-rate response of a Farmer chamber has been investigated up to the maximum achievable dose rate with such a gantry. For this, under reference conditions, the Farmer chamber in water was exposed to a 10x10x5cm^3 field centered at 10cm depth with different dose rates and dose levels.

Results: During PBS, pencil beam currents around 5nA at isocenter could be reached. Under these conditions, a single pencil beam could deliver up to 120Gy/s in water (figure 1). Faraday cup measurements showed no dose rate dependence of the PBM. Similarly, when the Farmer chamber was exposed to up to 100Gy/s and 8Gy, no significant dose rate dependence was observed.

Conclusions: Proton beams generated with a cyclotron, like in this work, can be considered as continuous and as such, dosimetry performed in the lower end of the FLASH domain do not appear to be particularly challenging.

PTC58-0021

Improving the dose distribution in minibeam radiation therapy: Protons vs helium ions

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Purpose: Hadron minibeam radiation therapy combines the improved dose deposition of ions with the normal tissue sparing of submillimetric, spatially fractionated beams [1,2] thus enabling safe dose escalation in the tumor. Next to protons [3,4,5], helium ions are a possible choice for minibeam radiation therapy. They offer reduced lateral scattering without the problems of nuclear fragmentation encountered with heavier ions [6,7].

Methods: Proton and helium ion minibeams of the same range have been simulated in a water phantom and in CT images of a human head. The Monte Carlo simulation toolkit GATE v8.0 [7] was used. Two configurations corresponding to beam sizes of 1 and 3 mm (FWHM) at target entrance were considered. Different minibeam spacings were evaluated. The dose and lineal energy transfer (LET) were measured in the targets.

Results: Helium ions yield an improved Bragg-peak-to-entrance dose ratio (BEDR), especially for the 1 mm beams. At equal minibeam spacing, they lead to larger peak-to-valley dose ratios. The LET was higher for helium at all depths.

Conclusion: Helium ions might present the best compromise for minibeam radiation therapy offering an improved BEDR and less lateral scattering without the possible drawbacks linked to nuclear fragmentations.

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PTC58-0027

Ne-MBRT: A worldwide first implementation of spatial fractionation for very heavy ions

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Purpose: Very heavy ions had demonstrated their efficacy against hypoxic tumors [1]. Clinical results showed late adverse effects on tissues, which led to the discontinuation of very heavy ion therapy. Nevertheless, a renewed use by a combination with minibeam radiation therapy (MBRT) might lead to a considerable gain in tissue sparing, allowing a safe use of the therapy while profiting from its advantages [2]. Our previous Monte Carlo studies indicated favorable dose distributions, with Ne ions leading to a more balanced dose and LET distributions compared to other types of heavy ions [3].

Methods: 230MeV/n of Ne minibeams were produced and evaluated at the biology port of Heavy Ion Medial Accelerator (HIMAC), Japan. Dose distributions were measured using gafchromic films and a microdiamond detector. Irradiations of normal human fibroblast cells were performed both in conventional and in MBRT modes with the same average dose, to assess possible differences in terms of viability, pro-inflammatory cytokines production and infrared spectroscopy.

Results: The dosimetry evaluations show the feasibility of our implementation (see figure 1). Differences in terms of pro-inflammatory cytokines production between irradiation modes were evaluated.

Conclusion: We have performed the first worldwide implementation of Ne-MBRT at HIMAC. Our preliminary results show the feasibility and the interest of this approach. [1] Castro et al., IJROBP 1994. [2] Prezado et al., Scie. Reports, 2017. [3] Peucelle et al. Med. Phys. 2015

PTC58-0059

Prospective data registration in proton beam therapy nation-wide evaluation trial (PROTON-NET) using unified treatment protocols with central and onsite monitoring

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Purpose: To evaluate the basic data quality of PROTON-NET as a potential international source for establishing clinical evidence.

Materials and Methods: A national consensus was reached for the selection criteria, treatment protocols, and patient follow-up intervals with proton beam therapy (PBT) in 91 situations for 40 diseases at 9 tumor sites in 2015. A prospective data collection IT system has been developed and used for 2 years to collect a minimal clinical dataset. To receive reimbursement from the health insurance organization, all PBT institutions in our country must have fulfilled minimal requirements including use of the same selection criteria of patients, to enable discussion in the institutional cancer board which consists of surgical, medical, and radiation oncologists, to use the same treatment protocols, and to register all adult patients into the IT system. Data management was performed by an academic data center. Central monitoring using IT and on-site face-to-face monitoring was conducted at all institutions by an academic society.

Results: The central and on-site monitoring have shown that all institutions fulfilled the minimal requirements. There were 4,842 PBT patients registered from the 14 institutions between 2016 May 1st and 2018 June 30th. Excluding patients with prostate cancer, the local control rate, progression-free, and overall survival at 12 months was 90.1%, 60.7%, and 95.5% respectively. Grade 3, 4, and 5 late toxicity (CTCAE ver.4.03) was observed in 38 (1.6%), 3(0.1%), and 2(0.1%) patients respectively.

Conclusions: The quality of PROTON-NET was shown to be reliable as a basis for establishing clinical evidence.

PTC58-0259

Exploring the potential of a fixed proton beamline fully integrated into a conventional treatment room for photon therapy

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Purpose: Proton Therapy (PT) is a limited resource that is not available to all patients who may benefit from it. We explore the potential of a new cost-effective design for PT, which may facilitate proton treatments in conventional treatment rooms and allow the widespread use of protons.

Material and Methods: We consider the following design: The treatment room consists of a standard Linac for IMRT, a motorized treatment couch to treat the patient in lying position, and a horizontal proton beamline equipped with pencil beam scanning. With this setup, proton plans may be sub-optimal as beam angles are limited to a coronal plane. However, high-quality treatment plans may be realized by delivering protons and photons in the same fraction. Treatment planning is performed by simultaneously optimizing IMRT and IMPT plans based on their cumulative physical dose. We demonstrate this concept for a head and neck cancer.

Results: Figure 1 illustrates the proton and photon dose contributions in an optimal combination and their cumulative dose. Figure 2a compares the DVHs for the proton and photon dose contributions. Photons are used to improve dose conformity while protons allow reducing the integral dose to normal tissues. In fact, the combined treatment improves on both single-modality IMRT and IMPT plans (Figure 2b) and achieves 74% of integral dose reduction in normal tissues that the IMPT plan yields.

Conclusions: Affordable PT systems will likely include a fixed beamline rather than a gantry. Proton-photon combinations may retain high treatment quality while making protons available to more patients.

PTC58-0677

Creation of proton minibeams using single quadrupole Halbach cylinders

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Proton minibeam radiation therapy (pMBRT) allows normal tissue sparing by utilizing an array of beamlets to deliver a spatially fractionated proximal dose that blends into a homogeneous dose at the target. These elliptical beamlets have very narrow lateral dimensions (<= 1.0mm) typically produced using precision collimators or MLC's. However, the use of these beam shaping devices can negatively impact dose rate and lead to the production of extraneous secondary particles. In the present work we investigated the potential of using a single magnetic quadrupole to produce the planar proton minibeams used by pMBRT. Monte Carlo simulations of unmodulated pencil beams with a 10mm initial diameter and 9.8cm range in water were focused with a single magnet of length 8.0cm and a field gradient of 250T/m. The combined dose distribution from five beamlets with center to center separation of 5.5mm and lateral FWHM of 1.2mm at 1.0cm depth showed high proximal spatial fractionation. The peak-to-valley dose ranged from 27.2 to 1.0 over 60% of particle range, and Bragg peak-to-entrance dose ratios for peaks and valleys were 19.2 and 0.73, respectively. At the level of the Bragg peak, the lateral beam dimensions were 2.7 and 2.6cm FWHM (Figures 1 and 2). This preliminary data suggests that magnetic focusing in pMBRT can deliver dose distributions that are comparable and potentially superior to those generated using collimators or MLC's. Magnetic focusing technology for pMBRT can be applied both in passive and active proton delivery and is the subject of ongoing research.

PTC58-0030

Towards magnetically focused proton minibeams: Investigating the limits of a clinical PBS nozzle

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Purpose: Proton minibeam radiation therapy [1] seeks to promote normal tissue sparing through spatial fractionation of the dose, thereby widening the therapeutic window [2,3]. To maximise this effect, the beam width should be below 3 mm (FWHM) [2,6]. Currently, minibeams are generated using a multi-slit collimator [4,5], however, magnetic focusing will be necessary to increase dose rates, reduce neutron production and enable 3D intensity modulation. Towards this goal, a feasibility study based on a clinical PBS nozzle was conducted.

Methods: The Monte Carlo simulation toolkit TOPAS v.3.1.p02 [7] was used to model a complete PBS nozzle including the quadrupole and dipole magnets. The magnetic fields were varied and several geometry modifications were investigated to assess the focusing limits.

Results: Focusing limits of the current configuration were established: 12.3 mm at 100 MeV and 6.4 mm at 200 MeV. The beam size may be reduced considerably by adding quadrupole magnets (1.8 mm at 100 MeV, 1.4 mm at 200 MeV) or considering a more compact nozzle (1.1 mm at 100 MeV, 0.6 mm at 200 MeV).

Conclusion: It will be challenging to realise collimator-free generation of proton minibeams at current clinical beamlines. However, different approaches to obtain the required beam size are proposed.

References: [1] Prezado et al., Med. Phys., 2013. [2] Prezado et al., Scie. Reports, 2017. [3] Prezado et al., Radiat. and Oncology, 2018. [4] Peucelle et al., Med. Phys., 2015. [5] De Marzi et al., Med. Phys., 2018. [6] Prezado et al., submitted to Int. J. Radiat. Oncol. Biol. Phys. [7] Perl et al., Med. Phys., 2012.

General: New Investigator

PTC58-0414

Radiographer led daily cone beam CT anatomical match and online correction for adult tumor sites treated with proton beam therapy

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Background: In UK radiotherapy centers, radiographer-led or radiographer alone daily cone-beam CT (CBCT) matches is the standard of care. In the first UK Proton Beam Therapy center treating non-paediatric cancers, the concept of radiographer alone daily CBCT and 'on-line' correction has been implemented.

We compared the 'on-line' daily cone-beam CT matches and shifts performed by radiographers during clinical treatments with 'off-line' reviews carried out by oncologists.

Methods and Results: Our center is equipped with IBA Proteus®ONE proton therapy machine incorporating large field of view kV CBCT and 6D robotic table.

Every patient undergoes daily CBCT imaging with on-line matching to planning CT and 6D patient position correction carried out by treatment radiographers using IBA's adaPT Insight® software.

We reviewed daily matches and corrections made by radiographers with 'off-line' reviews by oncologists to:

1. Compare radiographer matches with those made by oncologists to determine the magnitude and range of changes (if any),
2. Adequacy of image quality to determine anatomical matches,
3. Anatomical changes that would prevent daily proton beam delivery or require re-planning.

Data will be presented from the first 15 non-paediatric cancer patients treated on Proteus®ONE in our center since commencing treatments in April 2018.

PTC58-0362

Survival and radiation damage analysis of human skeletal muscle cells after photon/ion irradiation: Experimental data and Monte Carlo simulations

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Skeletal muscles were rarely included in the studies of dose-response relationship of normal tissues after radiation therapy (RT), even if they surround the tumor location in many cases and their damage could lead to worsening of complex functional endpoints (e.g. urinary symptoms, fecal continence, sexual dysfunction, dysphagia).

Recently, our group used texture analysis of T1&T2-weighted images to investigate RT-induced changes in the pelvic obturator muscles (Scalco Med Phys 2018). A clear exponential relationship between mean signal intensity and local RT dose was found, thus supporting the hypothesis that imaging can be used to objectively determine muscle insult induced by RT.

This new project, funded by the National Cancer Institute in Milan, aims at investigating the radiation response of human skeletal muscle cells (HSkMCs purchased from commercial vendors, never used in this context so far), both by in vitro experiments on cell DNA-damage and cell survival, and by Monte Carlo simulation.

Specifically, we will determine the radiobiological parameters of HSkMC upon irradiation with photon and proton/carbon ion beams at several dose points. Cell survival data will be compared with the outcomes of a simulation code modified ad hoc to deal with HSkMCs (Ballarini and Carante Radiat Phys Chem 2016). A second set of experimental measurements will include kinetics of γ-H2AX foci and apoptosis detection; this will provide further information to be included in the code.

Because the number of patients treated with hadrons is still limited, we can expect that radiobiological understanding of muscle response could help to identify constraints for hadron treatment planning.

PTC58-0419

The project NEPTUNE (Nuclear process-driven Enhancement of Proton Therapy UNraVeled)

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Recently an increase of proton therapy effectiveness for irradiations occurring in the presence of 11B atoms has been observed. A role in this effect should be played by the high-LET alpha particles mainly generated by the p(11B,a)2a channel, which has a cross section of the order of 1 barn at very low incident proton energy. However, analytical calculations indicate that the number of alphas produced is too low to yield the observed biological effects.

The Italian INFN institute recently funded a project called NEPTUNE (Nuclear process-driven Enhancement of Proton Therapy UNraVeled) with the main aim to study and understand this radiobiological effect.

The main objectives of NEPTUNE will be the consolidation of these results, extending them to include another nuclear reaction between protons and 19F and focusing on understanding all the physical and biological mechanisms involved. A physical characterization of the radiation field will be performed with tissue-equivalent detectors of various types, all based on micro- and nanodosimetric techniques. At the same time, biological measurements will be performed for different cell lines using several endpoints. New biological approaches will be to considered to study the problem from different points of view, which could reveal mechanisms not yet considered. All experimental data will be compared with predictions from analytical and Monte Carlo models.

The project is divided into four main Working Packages: WP1, modelling; WP2: imaging and quantification; WP3: microdosimetry and WP4: radiobiology. An additional group (WP5) coordinates all the foreseen experimental activities.

PTC58-0304

Quantifying DNA damage in comet assay images using neural networks

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Proton therapy for cancer treatment is a rapidly growing field as increasing evidence suggests it induces more complex damage in DNA than photons. Accurate comparison between the two requires quantification of the damage caused, one method being the comet assay. The program discussed here, based on neural network architecture, aims to speed up analysis of comet assay images and provide accurate assessment of the DNA damage levels apparent in them.

The comet assay is an established technique in which DNA strand breaks are spread out, creating a comet-like object, Figure 1. The elongation and intensity of the comet tail indicate the level of damage incurred. Many methods to measure damage exist, from "by eye" ranking systems to computer software, which can be time consuming. They result in analyzing only a small fraction of images, which is a problem addressed by this program.

The neural network performs object detection and localization using instance segmentation (Figure 2). Rather than extracting features to distinguish if and where an object is, instance segmentation incorporates the bounding-box method with pixel-wise classification, aiming to sort pixels into one of three classes: comet, background or contamination. The purpose is to provide accurate measurements of the comet tail length and tail DNA fraction, some common features used to measure DNA damage following a comet assay. Further, modelling of the comet assay process is underway to provide a better understanding of the relationship between the assay images and the underlying level of DNA damage.

PTC58-0691

Implementation status of carbon ion beam therapy at MedAustron

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MedAustron is a synchrotron based dual particle therapy facility, which started proton therapy in December 2016. Till end of 2018, 293 patients were successfully treated in 2 treatment rooms using fixed-beam lines. Early 2019, technical commissioning of a horizontal beam line for carbon ions has been completed, and medical commissioning is ongoing.

In July 2019, carbon ion radiotherapy (CIRT) treatments will start. Main beam properties are: 242 energies from 120-402.8MeV/n (ranges in water from 2.9cm-27cm in 1mm steps – Figure 1), spot sizes (in FWHM at isocenter in air) from 6mm (402.8MeV/n) to 10mm (120MeV/n) and maximum field size of 20x20cm^2.

The patient positioning system is designed for non-isocentric setups, allowing treatments close to the nozzle and reducing uncertainties in dose calculation with range shifter mounted in the fixed nozzle and pencil beam algorithms (Figure 2). RayStation8B (partly developed based on MedAustron requirements) will be commissioned for CIRT planning based on LEM I as RBE model.

In the first two years established Japanese protocols will be followed. A hypo-fractionated schedule (16 fractions) will be used for H&N non-SCC cancer, sarcoma and local recurrence from rectal cancer. Dose will be adapted after correction for RBE models. With the availability of motion management, hypo-fractionated CIRT will later be used in pancreatic cancer patients with 12 fractions for locally advanced cancer LAPC and 8 fractions for preoperative treatment. HCC will be treated with 2 fractions only. Spine and skull base chordoma will be treated with 3 GyRBE per fraction according to German protocols.

General: New Investigator Poster Discussion Sessions

PTC58-0466

New designs of electrostatic lens systems with quadrupole multiplets for production of sub-micron ion beam

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We have initiated an inter-university effort for the reconstruction of a new sub-micron ion beam to unravel the far-from-solved fundamental mechanisms in the ion-induced-damage of cellular matrix involved in heavy ion therapy. To obtain a sub-micron beam at the Gaussian image plane with a 30μm object aperture, we have designed two electrostatic lens systems and compared their performance with that of the electrostatic quadrupole sextuplet (EQS) currently employed at the micro ion beam facility in Columbia University[1].The design and simulations were done using SIMION 8.1® and GICOSY with both software benchmarked by accurately reproducing the experimentally measured parameters of the EQS. With an emittance of 0.2μm-mrad at the object aperture for 3MeV/q ion beams, our designed electrostatic quadrupole triplet (EQT) is capable of providing a high demagnification of (D_f) of 89.4 at a working distance (D_w) of 170mm, while the designed electrostatic quadrupole quadruplet (EQQ) gives a D_f of 32.5 at a D_w of 98mm. In comparison, the Columbia EQS[1] lens system has a $D_f \sim$ 38 at a D_w of 126 mm under the same input conditions. The physical lengths of EQT, EQQ and EQS are 0.835m, 0.850m and 3.887m, respectively. Apparently, the EQT achieves a higher demagnification with a more compact lens design and fewer quadrupoles. Our study also shows that with beam distortions at the image plane due to spherical aberrations (for divergence upto 0.03 mrad) and chromatic aberrations (δE/E upto 3.0E-4), EQT still produces a sub-micron beam at the target, indicating its stable performance.

PTC58-0660

Robustness metrics for two different beam arrangements in IMPT for nasopharyngeal cancer

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Aim: We analyze robustness of two IMPT beam arrangements towards rigid shifts and range uncertainties using robustness metrics. A ‘‘standard’’ three-beam arrangement is compared to a five-beam split-field technique which will be standard practice at our coming proton therapy facility.

Methods: Two robustly optimized IMPT plans (68/60/50Gy SIB) were generated using Eclipse (v13.7) for five nasopharyngeal cancer patients: three fields (two anterior-oblique, one posterior) or five fields with split targets (one anterior, two anterior-oblique, two posterior-oblique delivering dose only ipsilaterally; fig.1). Robust optimization parameters for target volumes, upper pharyngeal constrictor, and contralateral parotid were ±4mm shifts along cardinal axes and ±3% range errors for both plan types. Two robustness metrics were calculated: area spanned by error-scenario DVHs (A_{DVH}), and best-to-worst-case difference ($Diff_{BW}$) of relevant DVH metrics. For both, smaller values indicate higher robustness.

Results: Mean A_{DVH} for all targets was 27.6%, 25.3%, and 30.9% smaller for 3-field plans than for 5-fields (fig.2), and mean $Diff_{BW}$ of dose covering 99% (high-risk) or 98% (intermediate/low-risk) differed <0.1Gy between plan types. For brainstem and pharyngeal constrictor levels, mean A_{DVH} was smaller for 3-fields than for 5-fields (3.5% and 35.3/21.3/8.5%). For spinal cord and both parotids, mean A_{DVH} was 38.8% and 6.3/4.2% larger for 3-fields. For brainstem and spinal cord, mean $Diff_{BW}$f or dose to the hottest 1cc (D_{1cc}) was 14.7/15.8Gy and 14.1/13.7Gy for 3-fields/5-fields.

Conclusion: Minimum target coverage is equally robust toward shifts and range errors in both plan types, but for higher doses 3-fields are more robust. For OAR, A_{DVH} differences indicate robustness varies for different anatomical regions.

PTC58-0709

Implementation of an internship program as a new clinical methodology and practice

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The standard progression into dosimetry begins as a radiation therapist. Individuals make a natural transition into dosimetry where enrolling in an educational program and taking the MDCB exam were both optional in the United States. Three years ago, completing a dosimetry program to sit for the MDCB became a requirement, essentially removing the option for on-the-job training and self-learning. With this change, the option for many therapists to segue into dosimetry was eliminated based on the location of many of the educational institutions as well as the financial aspect related to the decision of shifting careers. A reduction in potential talent with an established background in an already small field, is an unintended byproduct of changes that are meant to raise standards. In order to foster continued education and development for current radiation therapists, an adoption of new methodologies is recommended to facilities. This new methodology would include creation of an internship program at facilities that are open to current radiation therapists. An internship program would not only benefit the radiation therapist looking to become a dosimetrist, but also the facility as a future investment. In particular to proton therapy, where planning techniques are different than photons and education on this topic in schools is very limited, an internship program would provide an invaluable bridge between therapy and dosimetry roles. The scope of this will include personal experience as an intern myself, as well as provide comparative data on online dosimetry programs with outcomes to brick and mortar institutions.

Physics: Beam Delivery and Nozzle Design

PTC58-0721

Study of treatment duration as a function of machine parameters for a proton pencil beam scanning synchrotron with multi-energy-extraction

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Mayo Clinic Rochester switched to treating with MEE in January 2018. The significant reduction in treatment duration due to MEE has been previously reported. There are several additional factors in synchrotron PBS which contribute to the irradiation time of a treatment field. They are: time to calculate delivered spot characteristics before delivering the subsequent spot (SCT); scanning magnet (SCM) speed; extracted beam current; charge in synchrotron; recapture efficiency between MEE energies; and time to switch MEE energies. To shorten the contribution to the irradiation time from each of these parameters would require modifications to the existing machine. To understand the significance of each parameter the recently published 4D dose calculator (Ref 1) was used to study the contribution of each of these parameters for two patients: a liver patient using repaint (RL) and a typical head and neck (HN) patient. For both patients reducing the spot calculation time has the greatest impact. The irradiation time is cut in half if SCT could be reduced to practically zero. Doubling the SCM Speed would reduce the irradiation time by about 10%. Doubling the beam current reduces HN by 15% and RL by 7%. Increasing the recapture efficiency from 50% to 99% reduced the irradiation time for HN by 9% and for RL by 12%. The impact of the combination of each of these parameters as well as the impact of the stored charge and time between MEE energies will be reported. 1) Pepin et al, Med Phys 45, (2018) pg. 5293.

PTC58-0109

A multi-cuboid ridge filter for optimized proton pencil beam delivery

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The purpose of this work was to design and optimize a multi-cuboid proton ridge filter (MCPRF) that can be used to increase the Bragg peak width in pencil beam scanning (PBS) treatments. Monte Carlo computer simulations were performed with the capability to insert or remove the MCPRF (Figure 1) and adjust device parameters including bar width (BW), bar spacing (BS), and filter thickness (FT).

Pencil beams of five monoenergetic proton energies (R50 of 51–103mm in water) were simulated and dose was recorded within a water phantom containing 0.25mm^3 voxels. Benchmark simulations were completed without the MCPRF in place to determine the PBS depth dose profiles and establish baseline full-width at 80% maximum (FW80M) values. From these simulations the relative Bragg peak weightings and FT could be determined theoretically and optimal parameters for the MCPRF were established. In subsequent MCPRF simulations, depth dose profiles were analyzed to quantify the impact of the MCPRF with varying design parameters on the Bragg peak FW80M. Lateral and 2D dose profiles were compared to those without the MCPRF to ascertain any unintended impact to spot size, spot shape or range uniformity. Results for 80–118MeV indicate that the MCPRF was effective at increasing the Bragg peak FW80M as compared to the baseline from 16-78% (Figure 2) without impacting beam spot quality.

The results presented here suggest that the MCPRF is an effective two-step range modulator for PBS applications that may be useful in minimizing PBS treatments times and improving beam delivery efficiency, especially for shallow targets.

PTC58-0145

Development and testing of a preclinical cone for magnetically focused proton radiosurgery

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High energy protons demonstrate beneficial dose deposition characteristics when treating small cancerous lesions including a low entrance dose, high dose Bragg peak and a well-defined range which limits integral dose. However, as beam diameter decreases below 1.0cm, beam broadening due to multiple Coulomb scattering (MCS) results in Bragg peak degradation that works against these advantages. Recent work in our laboratory suggests that magnetically focusing the proton beam immediately upstream from the patient could help compensate for the effects of MCS, potentially improving dose conformity and dose delivery efficiency for radiosurgical treatments. The purpose of the current project is to incorporate this technology into a pre-clinical beam delivery system for evaluation and testing at our facility. Similar to our bench-top design (Fig 1), the proposed cone (Fig 2) incorporates a triplet of quadrupole Halbach cylinders constructed from rare earth, radiation-hard Sm2Co17 permanent magnetic material with 10mm bore diameters and magnetic field gradients of 250T/m. The cone is optimized for dose delivery to small head lesions and has a form factor that mimics the stereotactic radiosurgery cone in use at our institution. Cone design and manufacture is currently ongoing and the latest results along with dosimetric evaluations will be presented. The use of the magnetically focusing cone as a drop-in replacement for a standard radiosurgery cone is expected to provide a simple and robust avenue to reduce entrance dose and beam number while delivering dose to millimeter-sized radiosurgery targets in less time than unfocused collimated beams.

PTC58-0097

Method for improved accuracy and speed from spot scanning systems

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Pencil beam spot scanning magnets, whether combined X-Y or separate, typically use laminated iron-yokes energized by four-quadrant power supplies. Practical limitations such as magnet yoke hysteresis, eddy currents and power supply bandwidth affect the spot positioning accuracy, stability, reproducibility and speed. This is turn can affect dose conformity and treatment times.

Adding a small correction X-Y magnet with deliberately small bending power (a few mm shift at full energy) but high speed, placed before the main scan magnets, produces a hybrid scan system with more nearly ideal behavior. The magnet is distinguished from a conventional beamline steerer by having very low inductance and use of features like ferrite return yoke and single layer high current coils. Its control is tightly linked to the scan magnet control. The deflection of the combined system is the sum of the main magnet and correction magnet to very good approximation.

Using the correction magnet and feedback from main scan magnet fields or measured spot positions as necessary allows the following to be performed in real-time:

- correction of small position errors caused by hysteresis
- compensation of small drifts in position due to eddy current decay, beam trajectory change or power supply instability
- faster settling of position by compensating over or undershoot of the main field
- deliberate blurring of a beam spot to increase its effective size and thus reduce the number of spots needed

PTC58-0561

Novel beamline diagnostics for proton beam facilities

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Beam diagnostic elements have been designed by PSI and continuously improved ever since the start of the PROSCAN proton therapy facility in 2007. In 2018, a Swiss company (AAT) developed new monitors based on the original PSI detectors, incorporating experience gained from many years of PROSCAN operation. State-of-the-art instrumentation development and engineering helped to optimize performance and control system compatibility.

The Profile Monitor is a retractable multi-strip ionization chamber (MSIC). It consists of a stack of specially patterned, metalized ceramic plates in a box filled with ambient air. Profiles are measured in both orthogonal planes (x/y) with a resolution of 1 mm in the central area and a lower resolution of 2 mm in the outer beam areas.

The Current Monitor is an ion chamber formed of a stack of five 5μm Ti foils. The outer and the central foils are connected to the HV supply. The other two foils deliver two independent and redundant current signals.

The CoM/Halo Monitor is an open bore ion chamber set-up with segmented pick-up rings. It provides a continuous monitoring of the beam centering.

A new multi-channel wide-gain pico to micro current amplifier has been developed to acquire data from the three detector types. It can be used with a standalone LabView application for testing and via a USB and Ethernet (TCP/IP) for beamline controls integration.

Tests have been performed with PSI's therapeutic proton beams with currents ranging 0.0...1.0 nA and energies ranging 70 ... 230 MeV.

PTC58-0292

A new treatment control system for a low energy proton therapy fixed beam line

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MEDICYC is a 65 MeV isochronous cyclotron at Center Antoine Lacassagne (CAL) in Nice, France dedicated to treating ocular tumors using proton therapy. Treatments are delivered by means of a fixed beam line and single passive scattering. MEDICYC performs on average 1200 treatment fractions per year, and consistently achieves treatment durations as low as 10 s, and distal and lateral penumbrae of 0.6 and 1.4 mm tissue equivalent respectively.

A new treatment control system is being developed for MEDICYC to perform treatment planning, treatment delivery and beam quality assurance. The system complements the existing TPS EyePlan with functionalities such as dose/MU calibration, dose rate calculations and design of beam modulating accessories. It also provides the full functionality needed to safely deliver and monitor a treatment, including a record and verify system to organize and upload patient data to the delivery machine. Delivered dose is measured using a two-channel setup, and with an independent method based on the quantity of secondary radiation recorded during a treatment, developed in-house. Finally, hardware and software tools are provided to conduct the daily beam quality assurance and to analyze the results with respect to historical data.

In this presentation, the hardware and software design choices that were made to meet the objectives described above while meeting stringent criteria with respect to safety, treatment delivery accuracy and treatment efficiency and beam availability, are discussed.

PTC58-0150

Implementation of chair in fixed carbon-ion beamline to treat head/neck cancer at seating position: I. hexapod 6-axis parallel positioner

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Multiple fixed-beamline carbon-ion fields in patient's sagittal plane provided clinical acceptable target doses with carbon-ion high dose-gradient and enhanced radiobiological effectiveness. However, non-planar fields with a 20-degree title angle to patient's transverse plane could achieve better dose-sparing of organs-at-risk. To have non-coplanar fields, a non-gantry solution by utilizing isocentric rotating chair as a patient positioner can be equivalently to a heavy/expensive gantry solution; having large 60-degrees title angle but is rarely used in actual treatments. Two distinctive conceptual approaches; referred as parallel (PM) and series mechanism (SM), were used to manufacture a positioner. The advantages and pitfalls using either PM or SM approach for a seating positioner was evaluated under the realistic constraints in our fixed particle beamline as shown in Fig 1. A robot system based on SM approach was found an interference occurring between robot arm and patient's leg rest. Based on PM approach, a compact Stewart Hexapod platform allows +/- 20-degree title but its translation displacement was highly reduced. By adding 3D translation and 360 rotation modules, combined Hexapod system can full perform the displacements over a 500 mm cubic treatment volume with 20-degree tilt and 360-degree rotation as shown in Fig. 2. For each subunit, its elastic deformation was simulation and its mechanical accuracy was evaluated by a laser-based tracking system. The validation of positioning accuracy for fully assembled chair was conducted to placing a head phantom at clinical treatment condition. An accuracy of $\pm$0.8mm and $\pm$0.6 degrees over 500mm treatment volume was achieved.

PTC58-0364

Study of optimizing treatment delivery with an add-on mini-ridge filter for synchrotron-based proton beam scanning system

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Aim: A synchrotron-based proton therapy system in the Shanghai Ruijin Hospital Proton Center is currently under beam commissioning. It consists of two pencil beam scanning treatment rooms (1 horizontal beam and 1 half-rotating gantry), one eye treatment room and one experimental room. To reduce the number of energies to generate a smooth SOBP while minimizing the impact of plan qualities, the design of an add-in mini-ridge filter (MRF) has been studied on the dose uniformity in the SOBP and beam delivery efficiency.

Methods: To reduce the total treatment time for large volumes or motion mitigation, different design of add-on MRF has been simulated in TOPAS. Using these simulations, Monte Carlo data were generated for TPS commissioning. For each design, dose uniformity, lateral and distal penumbras in water phantom or clinical case for shallow and deep target with and without MRF will be compared. Beam delivery time will be analyzed.

Results and Conclusions: For synchrotron-based proton beam scanning system, the use of an add-on MRF is significantly beneficial to reduce the number of energies to obtain a smooth SOBP and shorten treatment times for some cases. But the design and choice of MRF is important to balance treatment time and normal tissue dose.

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PTC58-0574

Dosimetric evaluation of range shifter designs based on beam data generated from GEANT4 code

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Range shifter is used in pencil beam proton therapy for treating shallow targets. It degrades the beam energy by shifting the spread-out Bragg peak close to the patient's surface. Our upcoming proton therapy system produces a nominal minimum energy beam of 71.3 MeV, which corresponds to a range of 4 cm in water equivalent thickness. In this work, Monte Carlo simulation with the GEANT4 code is used to simulate the beam data with three different thickness of range shifters for an asymmetry field size scanning range. The beam data of different proton energies are simulated in (i) voxel water phantom of 0.1 mm resolution to generating the integrated depth dose, and (ii) voxel air phantom of 0.2 mm resolution to calculate the beam spot size at isocenter. The beam data is input into Eclipse Treatment Planning System (version 13.7), to further evaluate the dosimetric impacts on a few clinical cases. Parameters such as homogeneity index and conformity index are used for quantifying the dosimetric differences of using these three range shifters. Since accurate modelling of range shifter allows us to calculate the beam spot size entering the patient, we would have better understanding of the implementation of range shifter in our pencil beam scanning system and avoid any potential pitfalls that may arise from our own design of range shifter. We foresee this work to be helpful for other upcoming proton centers that would use a similar system.

PTC58-0262

Study of parameters and errors affecting performance of synchrotron-based proton beam scanning system

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Aim: To optimize the overall performance of a Synchrotron-based Proton Beam Scanning System (SPBSS) during the commissioning, spot scanning parameters and errors in beam delivery has been studied extensively.

Methods: A synchrotron-based proton therapy system (Shanghai Advanced Proton Therapy project, SAPT) is currently under beam commissioning. A SPBSS simulation platform has been developed to calculate resulting dose distribution in water phantom or patient cases, as well as beam delivery time for specified parameters. Major parameters variations may cause dose error, including spot position error, beam size variation due to slow extraction spill characters and spot weight errors. Based on the GEANT4 Monte Carlo calculations and beam measurements data, a set of data libraries and parameters, which represent the various combination of major performance or error contributors, has been determined and used as base data for the treatment planning system-matRad[1] and SPBSS simulation. Their individual and combined effect against treatment planning spot configuration and optimization method on the dose distribution is quantified.

Results: The configuration of SPBSS and treatment planning parameters are trade-offs between the system reliability, treatment efficiency and plan quality. Comprehensive relations between selected parameters are visualized with plots.

Conclusions: To speed up the commissioning as well as provide a baseline for machine tuning, the relation between those TPS parameters, imperfections of beam delivery system and resulting dose errors has been studied to find optimal configuration sets for performance optimization of representative treatments.

PTC58-0699

Analysis of treatment planning statistics for the first Mevion HYPERSCAN proton therapy system

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Purpose: To analyze the first 9-months of system data from the first clinical HYPERSCAN (S250i) system to determine the extent of the treatment space being utilized.

Method: Anonymized DICOM Plans and Records for the first 9-months of treatment have been collected and analyzed for content. This includes investigating the number of treatment beams for each plan, as well as the typical energies and treatment angles most used by these beams. The plans were also inspected for whether or not they utilized the Adaptive Aperture.

Results and Conclusion: There were 156 beam fields analyzed spanning March to December of 2018. The typical treatment plan for the first S250i system contained 2 treatment fields (average 2.17) and all beams utilized the adaptive aperture for a sharper penumbra. The most common treatment angle was a 90-degree lateral, followed by 155-160 degree posterior obliques (see Fig 1). Despite the nominal 227MeV energy of the Mevion S250i system, the highest energy used in any treatment field was only 213MeV and in excess of 95% of beams were delivered entirely using energies of 200MeV or less (see Fig 2).

At the highest level, the treatment plans prescribed for the Mevion S250i system are quite similar to those most commonly employed by the original Mevion S250 scattering system in number of beams, treatment angles and energies used. Anonymized DICOM treatment plans and records can be a valuable tool for generating treatment statistics for making efficiency optimizations and future design considerations.

PTC58-0152

Response to ambient temperature of a dose monitor in particle beam therapy

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Background: For a vented ion chamber, the output varies depending on changes in both temperature and barometric pressure, so it is necessary to correct its output. The ambient temperature is adjusted to be constant using the air conditioner, but it may change somewhat depending on the operation state of the equipment used for the particle beam therapy. We confirmed whether the change in monitor output due to ambient temperature can be represented by well-known atmospheric correction coefficient.

Methods: Under certain irradiation conditions, the absorbed dose per dose monitor output (Gy/Count) can be obtained by a combination of a dose monitor (a vented ion chamber) located at the snout and a Farmer type ion chamber placed at the isocenter. The temperature of the location of the ion chamber of the Farmer type was kept almost constant, and the output (Gy/Count) was measured by changing the temperature near the dose monitor by operating the air conditioner. Regarding the temperature near the dose monitor, the sensor of thermometer was located in the place as close as possible.

Results: A considerable time delay was seen in the change in output of the dose monitor compared to the change in ambient temperature.

Conclusion: Chambers require time to reach thermal equilibrium with their surroundings. In a situation that the ambient temperature is changing, therefore, an appropriate correction should be necessary considering the time response determined from the positional relationship between the dose monitor and the thermometer in the irradiation equipment.

PTC58-0008

Design and test of an octupole scanning magnet for proton therapy

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Proton beams have several features that make them very effective in radiation therapy applications. These include high dose localization as well as high biological effect around the Bragg peak. Moreover, magnetic scanning methods allow one to spread an ion beam to an exact image of a complex tumor shape. The ion scanning system usually consists of two magnets, each scanning horizontal and vertical directions independently. This paper discusses the design for a novel octupole magnet design that provides beam deflection over a dipole field which can be set up at any azimuthal angle in the volume of the magnet bore. A test of the static and dynamic performance of the octupole scanning magnet has been performed using Hall probes and coils to measure the field inside the magnet and the results are presented in this paper.

PTC58-0201

Managed Beam Service (MBS) provided by Muir PT: A novel way of delivering proton beams utilizing mechatronics

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The current beam delivery system serving multiple treatment rooms has been a fixed accelerator (cyclotron/synchrotron) extracting a beam into a fixed beam line going to a number of adjacent treatment rooms, usually 3-4. Most treatment rooms have rotating 360-degree gantries for flexible beam delivery. The 360 degree These gantries are large, expensive and not only do the treatment rooms need radiation shielding but so also does the beam line itself. This current delivery system traditional approach has a substantial upfront capital strain and high ongoing operational cost.

Muir PT is offering the first Managed Beam Service (MBS) using a new mechatronics concept to re-engineer the proton therapy delivery system - with an 20% current system80% reduction in physical size even for the standard 6 room modular configuration. All equipment including shielding is factory assembled and delivered to hospital site pre-certified. Lead time from order to delivery is one year. Muir PT will make the Managed Beam Service (MBS) available to Healthcare Providers on a pay-per-treatment basis at the equivalent per treatment cost of Photon Therapy; that is, on a pay per treatment basis. This Managed Beam Service (MBS) delivers is assured outcomes in a manner that avoids upfront capital strain for the Healthcare Provider and covers the facility's operations and maintenance cost.

PTC58-0160

Shorter treatment time by intensity modulation with a betatron core extraction

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The CNAO (National Center for Oncological Hadrontherapy) main accelerator is a synchrotron capable to accelerate carbon ions up to 400 MeV/u and protons up to 250 MeV. Three treatment rooms are available and are equipped with horizontal beam lines; one of the treatment rooms also features a vertical treatment line to allow additional treatment ports. All of the beamlines are equipped with a pencil beam scanning system for dose delivery. With such a dose distribution technique, particles are sent to different depths by changing the energy from the synchrotron and are moved transversally by means of two scanning magnets. The number of particles to be deposited in each position varies strongly within the same iso-energetic layer. In order to maintain the required precision on the number of particles delivered to each spot, the intensity is reduced when spots that require low number of particles are present in a layer. A method to shorten the irradiation time based on variable intensity within the same layer is presented. This method can be used also with a betatron based extraction scheme. The results of preliminary implementation and test are reported.

PTC58-0033

Development and dosimetry of the 25 MeV proton irradiation line of the PRECy platform for radiobiology studies

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In vitro and in vivo research platforms with protons that reflect patient's irradiation conditions are needed. A 25 MeV cyclotron usually producing radio-isotopes, was used for developing such a platform for radiobiology studies.

An homogeneous irradiation field with a suitable proton flux is obtained by means of an aluminum diffusion sheet, then is extracted in air. The size of the irradiation field is defined using collimators (from 2 mm to 18 mm diameter) depending on the radiobiological studies. To allow energy modulation of the proton beam, a set of varying Al thicknesses is used to obtain a power range of 4.03 to 24.85 MeV.

Various dosimetric measurements have been made to validate this platform. An accuracy of less than 4% was measured on the total dose deposition with a heterogeneity of less than 1% on the diameter of the irradiated field

In conclusion, experimental results demonstrate that our 25 MeV proton platform is operational and allows precision irradiation for preclinical research in vitro and in vivo with a dose rate ranging from 0.1 Gy / min to 50 Gy / s and a range in LET for in vitro measurement from 2 to 10 MeV/micron.

PTC58-0607

Advanced beam delivery technology for carbon ion radiotherapy

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Carbon ion radiotherapy (CIRT) has progressed internationally in countries such as Japan, China, Italy and Germany, with substantial clinical experience. The PTCOG particle therapy patient statistics data updated to the end of 2017 indicates that there were 25,702 patients treated with carbon ions. The National Institute of Radiological Sciences (NIRS) in Japan has been a leading center in the clinical application since 1994, and has treated nearly half of this total population, with 11,964 patients treated through March 2018, representing substantial clinical and medical physics experience. The Toshiba technologies have been developed with the close collaboration and experience of the NIRS.

Toshiba provides CIRT technology which features:

1) compact rotating gantry with superconducting (SC) magnets,
2) ultra-compact scanning system,
3) 3D fast scanning irradiation with energy variation,
4) respiratory-gated irradiation with markerless fluoroscopic tracking.

These devices make it possible to treat moving tumors with gating and fast rescanning, which is the world's first application with scanning beam (Figure 1). Toshiba also provided the CIRT rotating gantry at NIRS, which applies SC magnets in the beam line for more effective bending, allowing reduction of the overall size of the device; clinical operation of the gantry started in May 2017. Using SC magnet technology and the ultra-compact scanning system, the size of the gantry has been further reduced in the on-going projects for Yamagata University and Yonsei University to be comparable to proton gantries (Figure 2). This presentation will provide insight on these state-of-the-art devices for CIRT delivery.

PTC58-0108

Monte Carlo study of short-lived isotopes production for online dose verification in particle therapy

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Online dose monitoring in particle therapy is a crucial part of a modern era technology. Hadrons travelling through matter may interact with atoms using strong nuclear force. One of the results of these interactions are the beta-emitting isotopes with various lifetime. The 3D distribution of the resulted annihilation gamma rays is well corresponded with the initial Bragg curve. These events ultimately lead to the practical range and dose verification of the initial particle beam in matter.

In this study we simulated using Geant4 the production of short-lived (half-life $<$ 1 min) and long-lived isotopes from monoenergetic beams of protons and carbon ions in homogeneous phantoms of water, PMMA and ICRU tissue. In this study we demonstrate that the production of short-lived isotopes and its annihilation gammas is enough to be registered on the top of long-lived background for ideal detectors. We suppose that registration of gamma lines from short-lived isotopes between the spills of synchrotron extraction might be useful to reconstruct dose within the single spill inside the human body.

Overall, the online dose verification is a promising part of a modern era technology for particle therapy offering a great extent to currently existing quality assurance procedures. *In vivo* dose verification might be useful for designing new therapeutic schemes and regimes of particle therapy.

PTC58-0646

Normalization of secondary radiation doses in proton radiotherapy: Can we do it in a better way?

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Currently in the literature unwanted doses related to proton radiotherapy are normalized only to the treatment dose. This prevents a close comparison between different experiments since the results are strongly dependent not only on the experimental setup but also on primary beam energy, target size and location.

As a continuation of EURADOS WG9 study (Mojżeszek, 2017), environmental doses from stray neutrons and γ-rays for a PBS treatment technique were collected as a function of field size, beam range and modulation width. The experiment was carried out in the Cyclotron Center Bronowice (Poland) using TEPC (HAWK) and six rem-counters (WENDI-II, LB6411, a regular and an extended-range NM2B). Detectors were positioned around an RW3 (30cm x 30cm x 60cm) phantom at seven points inside the IBA gantry room with a PBS dedicated nozzle.

H*(10) strongly depends on the detector position, with the largest values along the beam direction. Furthermore, variations of neutron H*(10) were observed with changes in range and field size. H*(10) for 10cm^2 field size and 10cm modulation varied between 7.0μSv/Gy at range 15cm and 25.4μSv/Gy at range 30cm at 2.25m distance and 135-degree angle with respect to the beam axis. Moreover, the presence of a range shifter increases unwanted doses by almost a factor of 2.

The presented results may help in understanding H*(10) variation with beam parameters such as dose, energy, modulation width or field size and finally in the development of analytical models of secondary radiation doses implemented in treatment planning systems.

PTC58-0592

Dosimetric evaluation of commercial proton spot scanning Monte Carlo dose calculation in small fields for ocular tumors

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Motivation: Ocular treatment with proton therapy is conventionally delivered on a dedicated beam-line, providing the advantage of sharp lateral and distal dose-falloffs. Newer pencil beam scanning-only proton centers lack dedicated beam-lines and thus do not treat ocular lesions. We report the development of an extended-snout-applicator (ESA) that retrofits with spot scanning snouts to provide the dosimetric and physical benefits of a dedicated snout for ocular radiotherapy.

Methods: A commercial Monte Carlo (MC) dose calculation algorithm for proton spot scanning was compared to measurements with the ESA in water using a microDiamond detector, PinPoint chamber, and Gafchromic film. Output factor, range, and lateral profiles at varying depths were assessed for proton beams of range 4 cm and 6 cm in tissue and five small circular fields varying from 1.0 cm – 3.0 cm in diameter.

Results/Conclusion: Ranges of pristine Bragg peaks in water (R80) were found to agree to within 0.5 mm (RMSE = 0.2 mm) and 0.8 mm (RMSE = 0.3 mm) for 4 cm and 6 cm ranged beams, respectively, between measured and calculated R80 for all fields. Preliminary results show greater than 95% pass rate between all measured and calculated lateral profiles (gamma criteria: 2%, 2 mm). Initial analysis shows good agreement (within 3%) for output factors for both beam ranges for all but the smallest field size (under investigation), supporting clinical implementation of the ESA for the treatment of ocular tumors.

PTC58-0537

Design considerations of the range shifter in a scanning nozzle for the compact superconducting cyclotron SC200

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The compact superconducting cyclotron SC200 for proton therapy is designing by ASIPP and JINR will able to accelerate protons to the energy 200 MeV with the maximum beam current of 400 nA. The beam energy is modulated using a degrader, which can reduce the energy between 70∼190 MeV. In order to apply the pencil beam scanning (PBS) technique to tumors located proximal to the minimum range, a range shifter is needed to insert in the nozzle to degrade the beam energy. However, the range shifter will broaden the proton beam and effect the dose distribution in the patient. In this paper, a range shifter model designed for the nozzle of SC200 was introduced and its influence on the proton beam was studied in detail. First, the investigation of range shifters of various material composition affect spot size in different geometries was performed. Then, using the analytic approximation and Monte Carlo methods, the effects of the gap between the range shifters and the mounting errors on the proton beam were carefully evaluated. Moreover, the mechanical analysis of the PBS nozzle with range shifter was performed using the SolidWorks. The results show that the polyethylene is the desirable shifter materials and designed model can meet the clinical requirement. Besides, the results presented here may prove useful for range shifters design of other research groups.

PTC58-0210

End to end simulations of the Clatterbridge Eye Proton Therapy beamline

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The world's first hospital proton beam therapy facility, based at the Clatterbridge Cancer Center, UK has successfully provided treatment for ocular cancers over the past 30 years. A 60 MeV beam of protons is produced and transported through a passive delivery system which enables the precise delivery of uniform dose at the target site. In addition to the long history of clinical use, the facility supports a rich program of experimental work and as such, there is a need for an accurate and reliable simulation model to fully characterize the beam. We present recent developments of a complete end-to-end simulation model of the Clatterbridge beamline, from the extraction point of the cyclotron all the way to the treatment nozzle. A comprehensive model of the delivery system was developed using the Monte Carlo simulation toolkit Geant4 and expanded to include precise CAD models of the treatment beamline. Upstream of the treatment room, an extensive beam dynamics study was performed to determine beam parameters utilized with the accelerator design code Beam Delivery Simulation (BDSIM). Experimental measurements were carried out to validate the accuracy of the simulated beams of both codes and findings were implemented in the combined model. The consolidation of information of the entire beamline is achieved through the superior geometry modelling and beam transport capabilities of BDSIM and recent results are discussed. The final model is anticipated to be available for wide use as a verified, standard simulation model for all related work performed with the Clatterbridge proton therapy beamline.

PTC58-0512

Physical design of gantry delivery system for SC200 superconducting proton cyclotron

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The SC200 superconducting proton cyclotron is a key project supported by the local government of Hefei, China and the Chinese Academy of Sciences. The project is based on an isochronous superconducting cyclotron that provides a 200 MeV fixed-energy proton beam. Such energy can be continually adjusted between 70 and 190 MeV using a wedge graphite degrader. The proton beam is then directed through beam transport system into gantry. In this paper, we present a new isometric gantry with downstream scanning nozzle scheme. For a 360-degree gantry, a double-waist round beam at the coupling point ensures the gantry beamline optics remain identical at all angles of rotation. Based on waist to waist theory, Beam line reverse, Round-beam method and TRANSPORT code, the emittance, momentum spread and maximum field and gradient was therefore determined. Moreover, the orbit distortion correction has been calculated with response matrix and SVD algorithm based on Madx. The results indicate that its physical design is reasonable and feasible. It can transfer the proton beam from 70 to 200 MeV to isocenter with a momentum spread no more than 1%. Currently the main components of gantry delivery system have been completed, such as magnets, mechanical structure and treatment nozzle. The magnetic fields of dipole and quadrupole magnets have been measured by hall mapping system and rotary coil measuring system. Testing of the mechanical part of gantry has also been done, whose deviation at the iso-center is extremely accurate and meets the design requirements of less than 1 mm.

PTC58-0511

Research and development of beam transport system of SC200 superconducting proton cyclotron

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The dedicated new medical facility SC200 with one gantry treatment room and one fixed beam room is under development in ASIPP (Institute of Plasma Physics Chinese Academy of Sciences). A 200 MeV/500 nA proton beam will be extracted from an isochronous superconducting proton accelerator. And then the beam transport system will guide the accelerated beam to one treatment room at a time. To enhance compact form of beam line, the main trunk line based on the beam optics design will be achromatic by 63-degree dipole magnets for minimum area. The layout of beam transport system is mainly consisted of a series of discrete magnets such as dipoles, quadrupoles and steering magnets. The beam transport system also employs an energy selection system, including an energy degrader which can modulate the proton beam energy from 200 to 70 MeV continuously, two collimators which can adjust beam emittance to 16π mmmrad, and a momentum slit. Currently the main components of beam transport system have been completed such as magnets, degrader, beam monitors, gantry and treatment nozzle. Moreover, the magnetic fields of dipole and quadrupole magnets have also been measured by hall mapping system and rotary coil measuring system. Testing of the mechanical and control aspects of degrader, gantry and treatment nozzle system has also been done separately. In the next stage, we will focus on system commissioning such as the measurement of the beam profile, position, current, loss, energy and energy spread.

Physics: Beam Delivery and Nozzle Design Poster Discussion Sessions

PTC58-0111

Proton range uncertainty due to momentum deviation

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In an accelerator, dispersion relates beam momentum offset to positional beam displacement. Because spot position is continuously monitored during treatments using a spot position monitor (SPM) and large deviations abort beam delivery, dispersion at the SPM can set an upper bound on delivered momentum deviation. Our institution uses a Hitachi PROBEAT V synchrotron that delivers beams of 70 to 230 MeV to four treatment rooms with gantries. The SPM is in the nozzle, approximately 0.5 meters upstream of the treatment isocenter. We measured dispersion at the SPM by varying the magnetic field strengths of all transport line optics, which effectively changed the beam's momentum offset, δ. For all four gantries, dispersions of 230 MeV beams were measured for a gantry angle; in one gantry, dispersions of 70 and 140 MeV beams were also measured. Momentum offset corresponding to $\pm$1 mm shift was converted to fractional range uncertainty. When dispersion was approximately zero at the SPM, dose rate measurements were used to identify momentum deviation that could reach the patient. The measured dispersion was both energy- and gantry-dependent. Shifts in beam positions as functions of δ for 230 MeV beams are shown in Fig. 1 (a); range uncertainty varied from 0.4% to 1.9% across the four gantries. The corresponding plot for the three different energies is shown in Fig. 1 (b); range uncertainties varied from 0.7% to 1.1%. Future work will involve dispersion measurements at other gantry angles to set an upper bound of momentum deviation that can reach the patient.

PTC58-0178

Using non-linear beam optics to shape the lateral penumbra of a proton beam: Proof of concept

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Background: Pencil-beam scanning (PBS) is often used in proton therapy to allow for multi-field optimization with fluence modulation without patient specific field-shaping devices. PBS may, however, result in a larger lateral penumbra (LP) than techniques utilizing aperture blocks for field shaping. Beam apertures or MLCs, may be used to reduce the LP, but may also increase the ambient neutron flux. As an alternative solution, non-linear beam components can be used to shape the beam without introducing high Z components in the beamline. This study compares the LP of a pencil beam to an octupole-shaped beam.

Materials and Methods: A generic proton beamline with five quadrupoles and one octupole has been simulated using TraceWin for beam envelope computations and Monte Carlo simulations of the lateral beam distribution at the ISO-center (1.000.000 protons). All beamline input parameters, e.g. current, energy and beam spot sizes, are comparable to that of clinical delivery systems. The beamline was optimized for maximal sharpening of the lateral vertical penumbra. The lateral fall-off (LFO) is estimated by the 20%-80% distribution width.

Results and Conclusion: Examples of beam distributions and vertical beam profiles (VBPs) are shown in fig. 1. It is evident that the VBP changes from Gaussian-like to box-like when the octupole is switched on. The LFO for two energies, three spot sizes, and two octupole modalities are summarized in table 1. It has been demonstrated that with a simple beamline containing an octupole, the LP of a proton beam can be significantly reduced without using any collimation.

PTC58-0256

Stereotactical fields applied with a modified pencil-beam scanning nozzle and collimating apertures

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The small fields employed in stereotactical radiation therapy require sharp lateral dose gradients, which are difficult to realize with the proton pencil beam technique. This holds especially true to shallow-seated tumors which require a range shifting block for energy degradation. The current work demonstrates a technical concept based on a slight modification of the pencil beam scanning mode of the IBA Universal Nozzle. A range shifter (6.3 g/cm2) is inserted in the beam path mounted in the wheel originally designed for the double scattering mode with a distance to the isocenter of 171 cm. Collimating brass apertures were mounted in the Snout180 extension. Proton fields were delivered in a service mode disabling the interlocks of the clinical mode. Lateral profiles were measured with the Lynx2D scintillation detector in conjunction with RW3 build-up plates and with EBT3 film. A beam model of the nozzle was established in the treatment planning system RayStation. Dose distributions were simulated with the Monte Carlo dose engine of RayStation. The experimental results show an 80%-20% lateral dose fall-off of 1.4 mm – 1.8 mm in air and 1.9 mm – 3.0 mm for water equivalent depths between 5 mm and 56 mm. In the figure lateral profiles with a 130 MeV field, 3 cm square aperture and air gap of 5 cm are presented as an example (measurement indicated by red line [1.9 mm lateral dose fall-off], simulation by green line). The measured lateral dose fall-off agrees with the simulated one on average within 0.1 mm.

PTC58-0555

Comprehensive approach to reduce proton dose application time with PBS

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A reduction of the dose application time opens up new treatment options in proton therapy (PT), such as the treatment of mobile tumors during a single breath-hold, the efficient application of hypofractionation or to mitigate motion effects by rescanning. Ultimately, shorter irradiation times provide benefits for both patient comfort and the PT-workflow.

The irradiation time is primarily determined by the available dose rate at the iso-center. In addition, the duration depends on the reaction times of the fast scanning actuators as well as the time for the energy change. We will exploit the availability of high proton currents from the cyclotron and the minimal dead time of line scanning to optimize the field application time.

The PSI Gantry 2 provides typical energy changes faster than 100ms. The beam current from the cyclotron can be precisely modulated in less than 1ms. Beam intensity losses in the energy degrader system can be at least partially reduced at low proton energy with a different degrader material [1]. By combining the different technologies, our goal is to irradiate fields for small tumor volumes $<$250ml in less than 10s and to integrate it safely into clinical operation.

The effective irradiation time depends strongly on the geometry of the dose distribution, particularly so for re-scanning, which have dose-distribution with low spot doses that may benefit from line scanning [2]. Increasing the dose rate is particularly advantageous for high field doses such as hypofractionation. [1] A Gerbershagen *et al* 2016 *Phys.Med.Biol*. 61 N337. [2] G Klimpki *et al* 2018 *Phys.Med.Biol*. 63 145006.

Physics: Commissioning New Facilities

PTC58-0064

Commissioning of McLaren Proton Therapy System

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Introduction: McLaren Proton Therapy Center (MPTC) is equipped with a Radiance 330^{TM} synchrotron which is capable of pencil beam delivery (70-330 MeV). The treatment rooms are equipped with a robotic couch for patient positioning and half gantry for beam delivery. The in-room imaging system is capable of acquiring planar and CBCT images while mounted from an independent x-ray gantry.

Methods and Material: The ionization depth doses for 70 to 250 MeV were measured using PTW water tank and Bragg peak chambers. An IBA Lynx was used to measure the beam sigma at isocenter as well as at four different positions relative to isocenter. The IAEA TRS 398 protocol was used to calibrate the delivered dose. The dose distribution was verified using gamma index analysis. The dose calibration and dose distribution were verified by IROC Houston for a prostate phantom. The gantry mechanical isocentricity was measured using an in-house fabricated device. Isocentricity shifts are accommodated by correcting the treatment couch positions for gantry sag for various gantry angles.

Results: The ranges of proton beams are verified to be within 0.5 mm of the tabulated CSDA values. The spots circularity is verified to be within 10% in X and Y axis. The positional accuracy of the spots is within 1.5% of the planned map. The gantry isocentricity is within 0.5 mm radius after couch correction.

Conclusion: The gamma analysis of dose distributions had a passing rate of $>$95% for 2%/2mm. Independent verification by IROC has verified our beam delivery calibration and accuracy.

PTC58-0127

Radiation safety and workload determination at the Groningen Proton Therapy Center (GPTC)

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Purpose: The UMCG-PTCG facility opened in Jan-2018 as a two-gantry proton facility. We report on the validation of the MCNPX-MC-simulations (F.Stichelbaut [1]) based shielding design relative to measurements .

Materials and Methods The beam usage was determined based on manufacturer (IBA,Belgium) provided logfiles (Fig.1) for a mix of pediatric, intra-cranial and Head & Neck (shallow located) targets . We performed measurements and determined dose outside the treatment rooms as a function of the facility workload. Stray radiation levels were logged at pre-determined locations using a FGH-40 with an Wendi-2 neutron detector during beam-on time. The Wendi-data was correlated to beam usage data based on time-stamps. Measurements during beam-off time were used to correct for fluctuations in background radiation, as background dose rate fluctuations have the same order as the stray dose rate.

Results and Discussion The log-file analysis made it possible to monitor beam usage on a day-by-day basis. Our actual beam usage increased approximately three times compared to our initial case-mix (which included deep seated targets, such as lung, prostate). In part, this increase may be explained by changes in the patient case-mix, we treat mainly shallow indications (H&N, CSA), resulting in lower energies and higher losses in the degrader/ESS. However, even at this increased yearly workload the measured radiation levels around our treatment rooms are well below the MC-predicted level of 100μSv/year.

Conclusion: The MC based shielding calculation-based predictions are conservative, overestimating the shielding requirements, even if the shallow targets increasing the cyclotron workload are predominantly treated.1) F.Stichelbaut IBA, private communications.

PTC58-0307

Feasibility study of multi-vendor integration between Eclipse, Mosaiq and ProteusOne system

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Introduction: The popularity of compact proton therapy systems has increased in recent years, especially among existing established radiation oncology facilities that seek proton therapy as an addition to their service. With various combination of applications available from different vendors, this study aims to evaluate the workflow feasibility to integrate Eclipse treatment planning system (TPS), Mosaiq oncology information system (OIS), and ProteusOne proton therapy system (PTS).

Materials and Methods: The beam data acquired for existing TPS commissioning were entered in Eclipse TPS (version 15.5). In addition to depth dose curves and spot fluence profiles, Eclipse TPS requires beam lateral spreader (scanning magnets) information provided by IBA. Current Eclipse TPS provides nonlinear universal proton optimizer (NUPO) algorithm and proton convolution superposition (PCS) algorithm for optimization, and is capable for robustness optimization. Beam data validation is done by measuring absolute dose in a solid water phantom using a PPC05 parallel chamber. A prostate plan composed of two opposite lateral beams was created and imported into Mosaiq (version 2.64). The plan was delivered with IBA AdaptDeliver and dose distributions were obtained with MatriXX PT ion chamber detector array for gamma analysis.

Results: The absolute point dose measured in the solid water was 0.08 CcGE (-0.04%) different comparing to the TPS calculated dose. The average gamma analysis for the prostate plan at three different depths using 3% dose and 3 mm distance-to-agreement criteria showed 95% passing rate.

Conclusion: This study demonstrated that it is possible to integrate IBA ProteusOne with Eclipse TPS and Mosaiq OIS accurately.

PTC58-0385

Medical physics commissioning of SAPT therapy system

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A synchrotron-based proton therapy system in the Shanghai Ruijin Hospital Proton Center is currently under beam commissioning. It consists of two pencil beam scanning (PBS) treatment rooms (1 horizontal beam and 1 half-rotating gantry room), one eye treatment room and one experimental room. The accelerator and beam delivery systems are developed by scientists and engineers from Shanghai Synchrotron Radiation Facility (SSRF), Chinese Academy of Science, funded by Shanghai Advanced Proton Therapy project (SAPT). The Ruijin Hospital is responsible for the clinical. It's expected to be the first hospital-based proton therapy center for joint-research and development in China.

The PBS system has started commissioning in the horizontal-beam room before the end of 2017. The eye treatment system (cooperated with PSI, Switzerland) and rotation gantry has been installed and the commissioning is planned in the first half of 2019.

A brief overview of the SAPT therapy system, commissioning method and status will be reported. The therapy system performance and commissioning experience will be discussed.

PTC58-0568

What is the representative spot size to be used in the treatment planning system?

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Purpose: In Eclipse, a single spot size is defined for each energy, which is then assumed to represent the spot size for all positions and gantry angles with that energy. This work investigates the best definition of such a reference spot size.

Methods and Material: Measurements were performed on a Varian ProBeam facility using Varian (IAS), IBA (Lynx) and in-house scintillating-foil-CCD (CCD1) systems, and were compared using single central spots for 17 energies. Additionally, spot sizes were measured with the IAS for a central and 48 equally spaced spots over the full scan range (25x35cm) at 4 gantry angles (0°, 90°, 180° and 270°) and for 10 different energies. X and Y sigmas were then calculated for each, and the minimum and maximum sigma for each energy compared to the mean value and sigma of the central spot at 270°.

Results: The measurements with three devices show maximum deviations below 3% (Figure1). Table 1a summarizes the mean spot sigma for each energy and the difference of the max/min spot sizes compared to this mean. Sigmas of the central spots at 270°, and max/min differences to this, are reported in table 1b. X and Y sigma for all the measured spots deviate $<$9.5% from the mean value at the same energy, whereas when using the central spot at 270° as reference, deviations are up to 15% for high energies.

Conclusion: The energy specific mean spot size, averaged over 4 gantry angles and all spot positions, can be considered the most representative spot size for the ProBeam system.

PTC58-0047

Current status and future prospects of a carbon ion therapy facility project of Yamagata University

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Construction of seventh carbon-ion therapy facility in Japan, East Japan Heavy Ion Center, Faculty of Medicine, Yamagata University, is near completion. The building is 45 m × 45 m × 27 m cubic design, smallest facility in the world, and connects directly to general hospital. A main synchrotron accelerator (a maximum energy of 430 MeV/u) with newly designed dipole magnets is located on the basement floor. There are two treatment rooms, horizontal and 360° rotating gantry, on the 2nd floor. Rotating gantry is even smaller than NIRS gantry using the superconducting technique and shortened scanning system. We chose RayStation (RaySearch Laboratories AB) as the treatment planning system which has very fast dose calculation engine to accurately calculate dose. In 2019, building construction and system installation will be completed, and acceptance testing and clinical commissioning will begin. After the commissioning work, first patient will be treated in spring 2020.

PTC58-0681

Preliminary range validation of two proton calculation models in Eclipse

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The treatment planning system Eclipse offers two proton dose calculation models; analytical proton convolution superposition (PCS) and Monte Carlo (AcurosPT). The two models use different Hounsfield unit (HU) to stopping power ratio (SPR) conversion strategies and are therefore validated separately. PCS uses the standard HU look-up table (HLUT) to SPR, while AcurosPT uses a HLUT to mass density. The HLUTs are created from the same stoichiometric calibration and the calculation models are created from the same base data.

We present a preliminary range validation study. CT scans of a pig femur bone sample including marrow were acquired with a dual energy CT scanner, Edge (Siemens Healthineers, Forchheim, Germany) using Twin-beam mode. Pseudo mono-energetic images were generated with the Siemens Mono+ algorithm at 90 keV. The water equivalent thickness (WET) of the sample was measured at four different positions with a single proton spot at 220 MeV using a multi-layer ionization chamber (Giraffe, IBA Dosimetry). In Eclipse, the WET was determined by the difference in range between the integrated depth-dose curves with and without the sample for both models. All calculations were performed at the measurement positions and hereafter displaced by 1 mm in 4 directions perpendicular to the beam using robust evaluation and the Eclipse API. Both PCS and AcurosPT overestimate the WET with an overall average WET difference for PCS of 2.8% and for AcurosPT of 5.2%. Ongoing investigations are performed to further evaluate this by measuring through various homogeneous soft tissues as well as heterogeneous samples.

PTC58-0395

Commissioning of the synchrotron-based eye treatment therapy system in Shanghai Advanced Proton Therapy Project

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The synchrotron-based proton therapy system in the Shanghai Advanced Proton Therapy Project (SAPT) is now under commissioning in Shanghai, China. There are four treatment rooms (one experiment room, one eye treatment room, one fixed-beam treatment room and one gantry room) in SAPT. In collaboration with the Center for Proton Therapy (CPT) at PSI, the design of the eye treatment nozzle and patient position system is same as that of OPTIS2 at PSI. However, to adapt the double scattering irradiation system to the SAPT synchrotron accelerator and therapy control system, a new irradiation control and verification system has been designed and implemented. It's very important to keep the beam quality and safety as same as the original system in PSI. For the patient, it's also important to keep the treatment time as short as possible while the SAPT synchrotron is quite different with the cyclotron and degrader at PSI. This report will introduce the overall design, implementation and preliminary commissioning result of the eye treatment room. We expect this treatment room will be the first dedicated proton eye treatment room in China.

PTC58-0736

Scanned proton beam performance and calibration on the Shanghai Advanced Proton Therapy Facility

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The Shanghai Advanced Proton Therapy Facility (SAPT) is a hospital-based facility constructed since December of 2014 and the first scanned proton beam line with a fixed horizontal nozzle was commissioned in October of 2017. The energy of proton beam is from 70MeV up to 235MeV extracted from a synchrotron accelerator, and the maximal scanning area of 40×30 cm2 (U×V) can be attained at the iso-center. In this article, the proton beam commissioning activities and the dose calibration for primary monitor chamber are described. The beam performance qualities according to the IEC-62667 medical standard were investigated, including the spot size in air, spot position, depth dose curves, profiles with various energies in water, and homogeneity of the scanned field as well. Consequently, the performance of main dose monitor has been studied and calibrated with each pseudo-monoenergetic proton beam individually. The calibration procedure is similar to the IAEA TRS-398 recommendation but being applied to a different effective measurement point to enable determination of dose to water in the plateau region. The measured dosimetric parameters could be as part of the clinical commissioning and quality assurance program to treat the patient.

PTC58-0679

Commissioning a proton therapy pioneer facility in Spain

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A proton therapy center is under construction in Madrid as part of the two pioneer centers in Spain (46.5 Mhab, 500 000 km^2). It will be a Proteus one single room facility operated by the group Quironsalud-Fresenius (46 hospitals, 23 linacs, high complexity). The equipment will include a Mosaiq OIS, Raysearch TPS and a double energy CT scan. The equipment rigging has been performed on November 2018 and the first patient is planned at the end of 2019, with 3.5 years ramp-up to achieve figures in the order of 400 pats/year, including hypo-fractionated schemes. A team is being built with experts from abroad and internal training with a planned ratio of 27/400 staff/patients per year. National recommendations are being prepared by the SEOR (Spanish Society for Radiation Oncology). A combined approach is under discussion with other centers having a close schedule, with common initiatives to validate gold standard data, share human and material resources to optimize commissioning efficiency, to warranty training and to share expertise.

PTC58-0509

Beam commissioning of HIMM facility

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Heavy ion medical machine (HIMM) is the first Chinese heavy ion accelerator facility developed for cancer therapy. The facility contains two ECR ion source, a cyclotron injector, a synchrotron, 5 nozzles and the beam delivery systems. It can provide the carbon beam with energy from 120-400 MeV/u and intensity from 1e7 ppp (particle per pulse) to 1.2e9 ppp in each nozzle. The uniformity of the radiation field in the terminals is better than 106% after scanning. The results of the HIMM beam commissioning are reported in this paper.

PTC58-0172

Design the prototype of environmental inspection robot in radiation control area: An example of the proton therapy cyclotron control area

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In order to reduce the radiation dose of workers, The high-radiation control area monitoring and inspection work, need to consider the allowable value of personnel radiation, the current high-radiation control area relies on monitoring equipment to operate, but it still depends on the location of the photographic equipment, the image resolution, and its environmental changes such as temperature cannot be immediately sensed, and the most basic work, such as the cleaning of dust, still depends on manpower.

Therefore, this study proposes a cleaning robot that maps large indoor spaces using laser scanning and can avoid obstacles. The chassis of the robot has independent primary wheels and auxiliary wheels as power and support. Direct current is employed to power the vacuum cleaner and the robot's drive motor, to prevent power loss. An indoor facility undergoes three-dimensional laser scanning, and the cleaning space is then mapped through matrix graphics; The distance to the wall, measured by the laser rangefinder, is employed as a reference for the correction of the robot's movement. The proposed robot was shown to clearly identify obstacles through laser scanning and successfully avoid them during the cleaning process to complete the task along the pre-planned route. It can reduce the radiation dose of workers and monitor the high-radiation control area.

PTC58-0240

Clinical commissioning of heavy-ion treatment facility Osaka-HIMAK

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The purpose of this work is to ensure safe operation of the new carbon ion therapy system Osaka-HIMAK (Heavy-Ion Medical Accelerator in Kansai).

Osaka Heavy-ion Therapy Center has three treatment rooms. Two of them (room 2 and 3) have horizontal and vertical ports, and another one (room 1) has horizontal and 45-degree ports. The two ports in the same room share a nozzle, which includes dose monitors, range shifters and ripple filters, and moves between the ports rotating around the isocenter. The respiratory-gated irradiation system is introduced in the room 1 and 2, and in-room CT will be installed in the room 2. The clinical commissioning had been done for the patient positioning system, the respiratory-gated irradiation system (and method), the beam delivery (raster scanning) system, and the treatment planning system (RayStation Doctor for delineating targets and organs and evaluating dose distributions, and VQAPlan for planning). We adopt the mixed-beam model as the biological model for treatment planning, and the so-called Schneider's method to derive the conversion table between CT value and the relative stopping power ratio.

The clinical commissioning of the room 3 had been completed by 15 October 2018, and the first treatment was carried out in 16 October. The treatment in the room 1 and 2 were also started sequentially after the clinical commissioning of each room was completed.

The eleventh carbon ion therapy facility had safely started the treatment in October 2018.

PTC58-0650

Preparing for helium therapy

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Charged particle therapy utilizing helium ions is currently being discussed as a viable alternative to carbon therapy, particularly for pediatric therapy. Ongoing technological advances may provide novel designs of treatment machines compact enough to fit into facilities of the same size as for proton therapy. To understand the challenges and possible benefits of a helium facility, we started to investigate several aspects related to a helium beam line and treatment planning with helium beams.

A Monte Carlo model characterizing a heavy ion beam line, similar to equipment used in Japan and in Europe, was employed to investigate the properties of helium beamlets in air and in a water-phantom. The range in water, longitudinal and lateral dose profiles, as well as spot sizes and energy distributions of primary and secondary particles along the central axis were the first parameters to be investigated. The impact of (passive) beam line components, such as energy filters, beam profile and spot position monitors, resulting in additional scattering, secondary particle production etc., are being evaluated in detail. We will use the data to configure the 'matRad' treatment planning system in order to evaluate the clinical properties of helium therapy plans.

In the future, we plan to design and perform high precision clonogenic essays, and small animal experiments in order to determine the biological effectiveness of helium compared to protons and carbon ions.

PTC58-0518

Status and evolution of the TOP-IMPLART Project

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The TOP IMPLART is a compact proton linac dedicated to cancer therapy. The accelerator up to 150 MeV is under construction. It consists of a commercial 7 MeV proton Linac produced by AccSys-Hitachi, operating at the frequency of 425MHz, and of a 3-GHz medium energy segment using commercially available S-band RF power systems. This machine is characterized by a small output beam size, a short beam pulse width and a high repetition rate, making it similar to the electron linacs used for cancer therapy. The TOP IMPLART peculiarities results in a compact design with reduced facility and operating costs with respect to conventional accelerator employed in the cancer proton therapy systems. In this paper the state of the art and the objectives of the TOP IMPLART project are described.

PTC58-0078

Current status and future plan of HIMM in China

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A hospital-based tumor therapy facility HIMM (Heavy-Ion-Medical-Machine) was developed, and two demo centers of heavy-ion-tumor-therapy facility HIMM were built in Wuwei and Lanzhou, Gansu, China, respectively. HIMM Wuwei is the first homemade heavy ion accelerator for tumor therapy with independent intellectual property rights. HIMM Wuwei got the first beam in December 2015, and then received registration detection by the authorized third part including performance test, electrical safety test, EMC test, software (including treatment planning system TPS) test and environment test and so on. Since 2014 China Food and Drug Administration (CFDA) issued many new supervision regulations of medical devices. With thousands sets of medical electrical components, heavy ion therapy facility is considered the largest medical equipment in the world, and the registration detection is a huge effort and very time-consuming. HIMM Wuwei passed the examination of CFDA and obtained the qualified report of the authorized third part in April 2018. According to the regulations of national medical device supervision in China, the clinical trials of 47 patients were followed after passing the registration detection. HIMM Wuwei started the patient treatment on November 6, 2018. The first clinical trials with carbon beams were carried at vertical+horizontal treatment terminal with uniform scanning and horizontal treatment terminal with spot scanning. The clinical trials of 47 patients are planned to be finished in February 2019, and the follow-up visit of three months will be followed thereafter.

PTC58-0487

Commissioning of the Shanghai Advance Proton Therapy

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Shanghai Advance Proton Therapy (SAPT) is a dedicated facility based on synchrotorn for cancer treatment in China. The commissioning of the accelerator started at the end of April 2017, and the proton beam has been already transported to the treatment room. This paper shows the commissioning results of synchrotron and transport line.

Physics: Commissioning New Facilities Poster Discussion Sessions

PTC58-0113

Physical characteristic measurements for the neutron beam generated by the linac-based neutron source for BNCT in University of Tsukuba

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Introduction: The University of Tsukuba is being developed a linac-base neutron source (iBNCT) for boron neutron capture therapy (BNCT). The device had been completed to produce and we have carried out the commissioning and conditioning to generate neutron beam with the high current proton beam. Fig.1 shows the linac of the iBNCT neutron source device. At present, various characteristic measurement experiments have been performed to verify the practicability and applicability of the neutron beam to actual clinical trials using the device.

Materials and Methods: Various neutron irradiation experiments with a rectangular water phantom were performed. For the measurement of the thermal neutron flux, gold wires were set inside the phantom. And many TLDs were also set in the phantom to measure gamma-ray dose rate distribution. In the experiments, average proton beam current was set to 1.4 mA. We had also evaluated degradation characteristic for beryllium target.

Results and Discussions: Both of the maximum values for thermal neutron flux and for gamma-ray dose rate were approximately 7.8 e + 8 (n/cm2s) and 1.8 Gy/h at 2 cm depth in the phantom, respectively. And the beryllium target had received over 2,000-coulomb proton beams until now, but neutron intensity has not decreased at all. This received proton amount is comparable to the amount that can emit neutrons that can treat more than 500 patients.The results for the experiments demonstrated the device can produce proper epithermal neutron beam applicable to BNCT treatment. Based on the results, we plan to perform the non-clinical study.

PTC58-0268

Clinical commissioning of the first proton therapy facility in India

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Our aim is to summarize the clinical commissioning of first proton therapy (PT) facility in India. The Apollo Proton Cancer Center (APCC) is a three-room PT facility equipped with ProteusPlus, Leoni 6D Robotic couch, RayStation-TPS and MOSAIC-OIS. ProteusPlus comprises a C230 isochronous cyclotron, dedicated pencil beam scanning nozzle, orthogonal kV-planar imaging and CBCT for image guidance. All tests related to electro-mechanical, safety, imaging and proton beam characteristics and their short-term reproducibility were carried out following protocol from IBA and the Atomic Energy Regulatory Board of India and results were within the prescribed tolerance limit.

The measurement of IDD, spot profile at different air-gaps, and absolute MU calibration were performed from 70.18-226.2 MeV in 5 MeV increment following recommendation of RayStation beam-modelling guide and were commissioned both for pencil beam and Monte Carlo algorithm. Mass-density to HU calibration curve of 85cm bore CT (AcquilonLB) were studied using CIRS head and thorax phantom for single and multiple inserts of inhomogeneity for three scanning protocol with and without metal artefact reduction algorithm and were commissioned in RayStation. Validation of TPS were performed through absolute and planar dose measurement. End-to-End test were performed using Head&Neck anthromorphic phantom. Accurate delivery of planned dose and stress test were performed for five clinical sites from AAPMTG-166 patient database. Planned and measured fluence at different depths agrees with gamma values of 3%at3mm above 95% (mean 98.3,SD=1.4).

The performance of PT facility at APCC is well within the prescribed limit and will provides an access to patients from India and neighbouring countries.

PTC58-0456

From commissioning to treatment with the ProteusOne at the Normandy Particle Therapy Center

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The Normandy Particle Therapy Center (CYCLHAD) began treating patients with the Center François Baclesse (CFB) in July 2018 using the IBA Proteus One solution after three weeks of acceptance testing and two-month commissioning. After 5 months, more than 20 patients have completed their treatment. The CYCLHAD center Proteus One is equipped with the IBA S2C2 (superconducting synchrocyclotron), a 220° compact gantry, stereoscopic imaging system and a 6D Leoni Orion System robotic couch.

This work summarizes and presents the various steps of the system characterization as well as machine and patient specific quality assurance (QA) program.

The proton beam system characterization and calibration presented were performed in order to comply with the RayStation treatment planning system (TPS) (RaySearch Laboratories) requirements:

- Integral depth dose (IDD) measurements
- Single spot measurements
- Absolute dose calibration

Among the validation tests presented, several volumes ($3x3x3cm^3$, $6x6x6cm^3$, $10x10x10cm^3$) centered at different depth were generated and compared to measurements with several detectors. Further testing with anthropomorphic head phantoms were performed.

Patient and Machine QA procedure, and the time needed to performed them, will be presented.

These validations tests and QA procedure ensure the reliability of the proton system for clinical activities.

PTC58-0458

Proton radiation beam matching and patient transfer workflow among rooms in a multi-vendor software environment: Conveniences, challenges, and potential solutions

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Purpose: Proton radiation beam matching option is available for a multi-room proton therapy center. The purpose of this work is twofold: First, as the first proton center to become clinical with a unique combination of RayStation, ARIA, and adaPT-IBA-system, we highlight the challenges and potential solutions for patient transfer workflow among different beam matched rooms in a multi-vendor software environment. Second, we present the comprehensive dosimetric results of proton beam matching for an IBA ProteusPLUS PBS proton system.

Methods: The measured proton beam matching parameters for each treatment room include: spot profile, absolute dose output, integral depth dose, range and modulation, and patient-specific QA results of various clinical cases. PBS proton and imaging (kV-planar and CBCT) machines are configured in RayStation, ARIA, and adaPT to facilitate patient transfer from one room to another.

Results: Although three gantries are beam matched dosimetrically, several challenges and potential solutions related to patient transfer among rooms were identified within ARIA and IBA system. Our current beam matching measurements include energies from 70-225 MeV with an increment of 5MeV. The spot size and range measurements among rooms were found to be within ±5%/±0.25mm and ±1mm, respectively, of each other. Absolute dose output was within ±2% with exception at lower energies. More comprehensive measurements at every 2.5MeV and various gantry angles are underway.

Conclusion: Beam matching provides the convenience of treating the same patient in any given room. However, patient transfer among rooms using ARIA and adaPT is non-trivial with several in-house solutions including changes in machine configurations.

PTC58-0494

Dosimetric verification at the Wuwei Heavy Ion Therapy Center using anthropomorphic phantoms

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The facility of Heavy Ion Medical Machine (HIMM) at the Wuwei Heavy Ion Therapy Center has passed the inspection of China's Food and Drug Administration. To demonstrate the suitability of the HIMM facility for clinical trial, dosimetric verification using anthropomorphic phantoms was conducted for treatment plans under the dose delivery with uniform pencil beam scanning. The head-and-neck section and thoracoabdominal part of an anthropomorphic phantom with Farmer chambers were scanned under a planning CT scanner with 1.5mm slice thickness, respectively. Using the two-set CT images acquired, virtual planning target volumes were delineated in ways that the chamber's sensitive volume was located in the center, proximal end and distal end of the target volumes, respectively. Then treatment plans were designed using a carbon-ion radiotherapy treatment planning system, which was dedicatedly developed for HIMM. The treatment plans were executed in the HIMM facility and dose measurements were taken. Additionally, respiratory signals were virtually produced and gating irradiation was conducted for a plan using the thoracoabdominal phantom. The deviations between the planned and measured doses were less than 1.70% for the centers of the spread-out Bragg peaks (SOBPs), 3.20% for the proximal positions and 5.44% for the distal ends, respectively. In the case of the respiratory gating irradiation, the dose divergence was less than 0.3% in the center of the SOBP; however, the irradiation time compared to that without gating increased by a factor of 2. Thus, the passive beam delivery of the HIMM facility dosimetrically meets the requirements for subsequently clinical trial.

PTC58-0556

Proton beam matching

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In conventional radiotherapy linacs are beam matched to allow patients to be treated on different machines for ease of scheduling or in the event of downtime. In proton therapy this has proved to be more difficult, in part due to the difference in hardware and the beam optics between the cyclotron/synchrotron and different treatment rooms. With the advent of standardised hardware for single room centers it may now be more feasible to beam match proton therapy gantries.

The beam properties that need to be matched include the spot size, shape of the Bragg peak, range, and dose per MU, all of which are as a function of energy. How well they match will determine if a patient can be treated at a different site for their entire treatment, a few fractions in the event of downtime or if a replan is necessary before any treatment.

We are aiming to have a network of proton therapy sites that are all beam matched with patient plans created using a single beam model. Measurements performed at three of the sites will show if this is possible or if patients could be treated for a limited number of fractions during downtime at one site.

PTC58-0569

Design and construction of accelerator-based boron neutron capture therapy facility with multiple treatment rooms at Southern Tohoku BNCT Research Center

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Purpose: To describe the design and construction of an accelerator-based boron neutron capture therapy (AB-BNCT) facility with multiple treatment rooms at the Southern Tohoku BNCT Research Center (STBRC).

Materials and Methods: AB-BNCT system at the STBRC is equipped with a cyclotron-based epithermal neutron source (C-BENS), which consists of a cyclotron accelerator (HM-30), a beryllium neutron production target, and a beam shaping assembly (BSA). We developed a remote patient transport system (RPTS) for workers to reduce the work time in the treatment room under the condition of remaining activities just after an irradiation. We studied the feasibility of this system and carefully designed optimum layout to realize patient flow and workflow efficiently.

Results: We designed the upside-down Y shaped beamline configuration, in which HM-30 and two treatment rooms are assumed to be located on a top and bottoms, respectively. To reduce the activities caused by thermal neutron, BSA is surrounded by LiF-loaded polyethylene blocks and low-activation concrete. The measured out-of-field thermal and fast neutron dose profiles were in good agreement with calculated ones using MCNPX. It was also confirmed that the RPTS could be operated up to 9 m apart from the RPTS without any problems.

Conclusion: We successfully established the environment of BNCT as one of a division of a general hospital without a sense of incongruity in comparison to an environment of conventional radiotherapy. The AB-BNCT system described in this study confirmed to specifications and is being used for BNCT in a hospital.

Physics: Absolute and Relative Dosimetry

PTC58-0203

GATE/Geant4 as a Monte Carlo simulation toolkit for light ion beam dosimetry

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Solid-state dosimeters are good candidates in light ion beam dosimetry due to the possibility of reducing the scoring volume down to sub-millimeter size. In contrary to ionization chambers, their relative effectiveness (RE) (i.e. energy and LET dependence correction) must be considered. The aim of this work is to determine the RE and the water-to-medium stopping power ratio ($s_{w,med}$), which are necessary to derive dose to water from detector signal. For this purpose, the GATE/Geant4 Monte Carlo simulation platform [1] is used. Several detectors (alanine, films and optically stimulated luminescent detectors (OSLD)) are studied in clinical conditions. An analytical expression for the $s_{w,med}$ was determined as a function of the energy deposition scored by GATE/Geant4 and the water and medium mass stopping powers of the particle. A new tool for the computation of the RE was implemented in GATE. The capabilities of GATE for the determination of $s_{w,med}$ have been demonstrated. For alanine and aluminium oxide (Al_2O_3), the $s_{w,med}$ is varying by up to 2% and 10%, respectively, over the depth-dose profile. Currently, the dose distributions corrected by the $s_{w,alanine}$ and $RE_{alanine}$ are being compared with those obtained with ionization chambers and alanine pellets (measurements acquired during medical commissioning of the proton beam line at MedAustron [2]). Subsequently, the validation of the $s_{w,alanine}$ and $RE_{alanine}$ calculation for the carbon ion beam line will be performed during the second quarter of 2019. References: [1] Sarrut, D., et al.” Medical physics 41.6Part1 (2014). [2] Carlino, A., et al. *Physics in Medicine & Biology* 63.5 (2018):055001.

PTC58-0426

Energy dependence of LiF detectors in proton beam dosimetry

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For patient dose monitoring purpose, the thermoluminescent detectors (TLDs) can easily report any interesting dose point as in-vivo dosimetry. However, the energy dependence may cause significant TLD measurement perturbation in proton beam dosimetry, especially for low energy beams. The purpose of this study is to evaluate the energy dependence on TLD measurement in protons.

Two types of TLD chips, TLD100 (LiF: Mg, Ti) and MCP100 (LiF: Mg, Cu, P) placed in HDPE phantom at 2 cm depth, were irradiated with 70-230 MeV of proton beams. The energy dependence was evaluated in terms of relative efficiency, which is the ratio of the emitted luminesce light intensity per unit dose for proton and 6 MV photon beam. The proton mean energy was calculated by GEANT4 Monte Carlo simulation code with various incident beam energies. The relation between the relative efficiency and proton mean energy can be established and used for energy dependence correction in proton beam dosimetry.

The measurement results from TLD100 and MCP100 were converted to relative efficiency. The relative efficiency of TLD100 and MCP100 in 70-230 MeV of proton beams ranged from 1.00 to 1.15 and 0.50 to 0.93, respectively. Accurate dose measurement using TLDs can be achieved by adopting appropriate relative efficiency correction, especially for different TLD types.

PTC58-0283

Development of a bone-equivalent material for the dosimetry of proton therapy beams

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Currently, tissue-equivalent materials have only been optimised for photons and electrons. Therefore, this research project has been proposed to develop tissue-equivalent materials that are suitable for proton therapy, so a uniform or anthropomorphic phantom can be created for the dosimetry of proton therapy beams.

So far four bone-equivalent materials, Hard cortical SB5, CIRS Cortical bone, Accura Bluestone and NPL bone material, have been compared to ICRP cortical bone at both 60 MeV and 200 MeV. Results have been calculated from an analytical model and FLUKA models which allow for the theoretical calculation of key dosimetric parameters; including mass stopping power, range, scattering length and fluence correction factors. SB5 and CIRS materials perform best out of the four materials. However, the results can have a 2-3% inaccuracy depending on what dosimetric parameter is being considered. Tissue-equivalent materials have been shown to be less tissue-equivalent at higher energies due to the increased difference in nuclear interactions.

The next stage of research is to test experimentally those currently available as well as newly developed materials against real bone samples with a proton therapy beam. Laterally integrated dose as a function of depth will be measured with ionization chambers in a water phantom. Gafchromic film (EBT3) will be used to investigate scattering properties. The test will obtain relative measurements of the bone-equivalent materials against cortical pig bone samples. These measurements will be compared to results collected via an analytical model and FLUKA model to determine the bone-equivalence of these materials.

PTC58-0436

Towards a synchrotron dedicated system for range control through Prompt Gamma Spectroscopy: Experimental results from p, He-4, C-12, O-16 beams

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Beam monitoring techniques aim to retrieve the position of the Bragg peak in the target in order to mitigate the planning limitations caused by the range uncertainties. This critical issue applies to all the beam species used in ion beam therapy. We propose the use of Prompt Gamma Spectroscopy (PGS) to provide on-line and in-vivo beam tracking for ^{1}p, ^{4}He, ^{12}C and ^{16}O beams. Our system includes a spectroscopic unit based on $CeBr_3$ and BGO scintillating crystals, a scintillating fibres beam trigger and an advanced FADC/FPGA data acquisition system for high speed digitalization. The development of the system focusses on the application of PGS in synchrotron-based facilities. Such system is applicable not only to the clinical beam species (^{1}p and ^{12}C), but also to the ones in research phase (^{4}He and ^{16}O) . The preliminary results show excellent performances in the detection of the gamma radiation over the full energy spectrum for all beam species (Figure 1). We observed a significant widening of the spectral lines when increasing the mass of the projectile, which should be attributed to the Doppler broadening. Moreover, we measured a strong correlation of the residual range of the primary ^{12}C particles with the intensities of the discrete reactions (Figure 2). Future work will include a complete characterization of the system and the systematic measurement of the energy dependent cross sections

PTC58-0552

2D radiophotoluminescence imaging for dosimetry of charged particle beams

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2D film dosimetry in charged particle therapy is important for mail auditing of proton therapy (PT) centers where 2D dose information is important to verify beam homogeneity and geometry and 2D imaging of the Bragg peak to check proton energy/range. Film dosimetry using the commercial gafchromic EBT3 films face challenges because of the density of ionizations i.e., linear energy transfer (LET), changes when penetrating through material. Luminescence materials have been studied as potential candidates for 2D dosimetry and radiophotoluminescence (RPL) detectors recently gained attention.

In SCK•CEN a stable 2D RPL dose scanning system was developed requiring limited corrections for image reconstruction, with a sub-millimeter spatial resolution (0.86 $\pm$ 0.10 mm). The Al_2O_3:C,Mg films demonstrated a dynamic dose response between 0.1 Gy and 100 Gy while the luminescence efficiency decreased as a function of high LET beams (^{1}H, ^{4}He, ^{12}C, ^{28}Si and ^{56}Fe).

The feasibility of 2D Bragg curve imaging has been demonstrated for a 61.3 MeV 40 mm diameter broad proton beam using a wedged phantom [De Saint-Hubert et al, Radiation Measurements 2019]. Next an algorithm is implemented to correct for the film's luminescence efficiency dependence with improved 2D Bragg peak imaging for an accurate analysis of the beam parameters. RPL sheets are irradiated in different PT beams and phantoms (wedged and stacked) in combination with Monte Carlo simulations.

The objective of this work is to demonstrate the feasibility of 2D RPL films (Al_2O_3:C,Mg) for optimized 2D film dosimetry in charged particle beams and its application in PT auditing.

PTC58-0393

Theoretical study of physical parameters of fundamental importance in reference dosimetry for hadron therapy

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The reference dosimetry in hadron therapy is based in the detection of secondary electrons generated by the ionization of the gas contained in ionization chambers. To determine the dose in liquid water, conversion factors such as W-values (mean energy expended by the incident particle to form an electron-hole pair after complete dissipation of its initial energy) in the gas of the ionization chamber are necessary. This physical parameter represents an important source of uncertainties in hadron therapy [1]. In a recent work [2] we studied the W-values by electron, proton and antiproton impact on vapor and liquid water. We used two different methods to take into account the slowing down of the primary particle and all the secondary electrons generated: the Monte Carlo code MDM (which does an event-by-event tracking of all particles, the primary and the secondary electrons) and the Fowler Equation (based in the Continuous Slowing Down Approximation). The results are in very good agreement with experimental data for water vapor and with values obtained by other authors for liquid water. In the present work, we calculate W-values by proton impact on the gases that compose the air extending the theoretical methods developed in [2]. Results obtained for proton energies from 0.5 to 100 MeV are in very good agreement with experimental data. In future work, these models will be extended to calculate W-values for other ions used in hadron therapy. References: 1) IAEA-TRS 398 (2005).

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PTC58-0471

Disagreement of measured small-field output with treatment planning system for a Varian ProBeam system

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Purpose: For pencil-beam scanning protons systems, in-air non-Gaussian halo can significantly impact output at small field sizes and low energies. Since the halo is typically not modelled in treatment planning systems (TPS), this can potentially lead to significant differences in planned and delivered treatment. Here, we report the magnitude of such disagreements.

Methods: A CC04 small-volume ion chamber was used to measure absolute output from a ProBeam nozzle in water, and the results were validated with a diamond detector. Field sizes from 2-20 cm were employed with energies ranging from 70-240 MeV. Measurements were taken at the water surface and at half-range for each proton energy. Raystation 8A's clinical Monte Carlo algorithm was used for output modeling.

Results: The extent of the halo is shown in Fig. 1, where plots at Z300 show the spot size just after the protons leave the snout, and Z0 shows the spot size 300 mm downstream. Fig. 2 shows the output measurements exhibit a 4-5% disagreement with the TPS for the 2 cm field with 100 MeV, and an 8% disagreement in output for the 2 cm field with 70 MeV.

Conclusions: We found that the clinical TPS overestimated output by as much as 8% for small field sizes of 2 cm at extremely low energy of 70 MeV. The in-air halo of low energy extension to 2-3 cm diameter may potentially lead to underdosage of patients treated with small fields.

PTC58-0231

A high throughput method for in vitro proton cell irradiation

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Background: Though proton therapy has become a well-established radiation modality, continued efforts are needed to improve our understanding of the molecular and cellular mechanisms during treatment. Such studies are challenging, requiring many resources. The purpose of this study was to create a phantom that would allow for multiple *in-vitro* experiments to be irradiated simultaneously with a spot scanning proton beam.

Methods: The setup utilized a modified patient couch top coupled with the robotic arm for submillimeter positioning. An acrylic phantom was created to hold four 6 well cell culture plates, at two different positions along the Bragg curve, in a reproducible manner. The proton treatment plan consisted of one large field encompassing all four plates with a monoenergetic 76.3 MeV posterior beam (fig. 1). For robust delivery, a mini pyramid filter was used to broaden the Bragg peak (BP) in the depth direction. EBT3 radiographic film was employed to validate absolute dose, using our in-house GPU-based Monte Carlo for LETd correction and provide secondary dosimetric evaluation.

Results: Due to beam divergence, variable proton path lengths in acrylic proximal to the cell plates resulted in film dosimetry $\pm$1.4% for dose delivered across the length of each plate at the BP, with negligible difference in the entrance region.

Conclusion: The proposed proton irradiation setup allows for four plates to be simultaneously irradiated with two different portions (entrance and BP) of a 76.3 MeV beam. Dosimetric uncertainties across the setup are within + 2%.

PTC58-0238

The doses of scattered photon and neutron on cardiac implantable electronic devices in scanning proton therapy to right neck

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Purpose: Patients with dependent cardiac implantable electronic devices (CIED) should avoid proton therapy to thorax due to high risk of malfunction resulted from secondary neutron production by proton beam. However, there was limited literature to evaluate the neutron dose on CIED in proton therapy for head and neck cancer. This study aimed to measure the doses of scattered photon and neutron on the surface site of CIED in scanning proton therapy to right neck.

Materials and Methods: A treatment planning of scanning proton therapy using right-anterior-oblique field and right-posterior-oblique field to treat right side head and neck cancer with 200cGy per fraction was adopted. On the bilateral infraclavicular surface areas of RANDO phantom, the Electronic Personal Dosimeters (DMC 3000 with Neutron Module) were set to simulate the ipsilateral and contralateral sites of CIED. We recorded the values of H_{10}-gamma and H_{10}-neutron detected by the dosimeters in proton therapy.

Results: The mean doses of H_{10}-gamma and H_{10}-neutron were 0.033 mSv and 0.530 mSv per fraction at left infraclavicular area and 0.024 mSv and 0.210 mSv per fraction at right infraclavicular area. Notably, both doses of scattered photon and neutron at left side were larger than those at right side despite the proton therapy to right neck.

Conclusion: The doses of scattered photon and neutron at bilateral infraclavicular areas were low; however, the doses at left side were unexpectedly larger than those at right side. The electrocardiogram monitoring during proton therapy and program analyzing after treatment should not be completely waived.

PTC58-0040

Reconstruction of physical and biological dose distributions of carbon-ion beam through deconvolution of longitudinal dosimeter responses

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Purpose: This is a theoretical simulation study for proof of concept of radiochromic film dosimetry to measure physical and biological doses without plan-based quenching correction for patient-specific quality assurance of carbon-ion radiotherapy.

Methods: We took a layer-stacking carbon-ion beam comprised of range-shifted beamlets. The dosimeter response was simulated according to an experimental quenching model. The beam model followed a treatment planning system. The beam was decomposed into finely arranged beamlets with weights estimated by deconvolution of longitudinal dosimeter responses. The distributions of physical and biological doses were reconstructed from the estimated weights and were compared with the plan. We also evaluated the sensitivity to measurement errors and to erratic delivery with an undelivered beamlet.

Results: The reconstructed physical and biological doses accurately reproduced the simulated delivery with errors approximately corresponding to the measurement errors. The erratic beam delivery was easily detectable by comparison of biological dose distribution to the plan.

Conclusions: We have developed a method to measure physical and biological doses by longitudinal dosimetry of quenched response without using plan data. The method only involves a general optimization algorithm, a radiobiology model, and experimental beamlet data, and requires no extra corrections. Theoretically, this approach is applicable to various dosimeters and to proton and ion beams of any delivery method, regardless of quenching or biological effectiveness.

PTC58-0619

Thermoluminescence sheet-type dosimeter for in vivo skin dosimetry in passive scattering proton therapy

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Purpose: Considering skin sparing is important in passive scattering proton therapy (PSPT), in which small number of fields may cause high entrance dose. *In vivo* skin dosimetry (IVSD) is desirable to perceive actual skin dose, however, the methodology of IVSD has not yet been established so far. Newly developed thermoluminescence sheet-type dosimeters (TLSD) are particularly suited for applications in IVSD because of their ease of use, and capability of adjusting size. We investigated the utility of TLSD for IVSD in PSPT.

Materials and Methods: Lithium triborate (effective atomic number 7.3) is the main component of TLSD (TOYO Medic Ltd., Tokyo, Japan). To evaluate the basic characteristics for proton beams such as dose linearity, uniformity, and energy dependences, unmodulated and modulated proton beams are irradiated to TLSD in parallel or perpendicular to the beam axis in the water phantom. Furthermore, to measure the actual range shift of the proton beam due to TLSD insertion in the field, the proton depth-dose curve measurements were obtained to determine water equivalent thickness (WET) with or without TLSD attached to the entrance wall of the water phantom.

Results: The dose response was found to be linear up to 10 Gy. The percent depth-dose and dose profile measured with TLSD well reproduced the results with ionization chamber. The WET without protective sheet was estimated to be approximately 0.2 mm.

Conclusion: Although there are some needs for improvement, the impact on range error is almost negligible in IVSD, new TLSD is suitable to be used as IVSD tools in PSPT.

PTC58-0423

Preparing for clinical translation of raster-scanning helium ion-beam therapy: Dosimetric validation with an anthropomorphic head phantom

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By 2020, the Heidelberg Ion Therapy Center (HIT) will launch the first clinical raster-scanning particle therapy program using helium ions (^{4}He), which exhibit favorable physical and biophysical properties intermediate of the clinically used proton and carbon ion beams. To support clinical operations, development of the first treatment planning system (TPS) for ^{4}He ions is currently underway. Recent works established a FLUKA Monte Carlo-based Treatment planning platform (MCTP) and an in-house GPU-based dose engine (FRoG) for the four ions available at HIT (^{1}H, ^{4}He, ^{12}C and ^{16}O). Preliminary validations compared spread-out Bragg peaks in water against measurements as well as patient dose calculations against gold-standard Monte Carlo simulations, demonstrating excellent agreement.

In this work, dose calculation and optimization performance is evaluated for ^{4}He ion beams. Through rigorous dosimetric study in clinical-like and worst-case scenarios (using the CIRS Proton Therapy Dosimetry Head Model 731-HN and a RANDO Alderson half-head phantom, respectively), both 1D and 2D measurements are acquired with a 24 PinPoint ionization chamber block and an OCTAVIUS® 1000SRS prototype detector. Dose prediction performance using both analytical and Monte Carlo methods for ^{4}Heion beams will be validated for the HIT clinic. Preliminary results (Fig. 1) demonstrate excellent agreement between FLUKA MC and FRoG against measurements, with absolute percent dose deviations 1.71($\pm$1.09)% and 0.84($\pm$0.61)% for FLUKA MC and FRoG, respectively.

PTC58-0449

Dosimetric comparison of techniques for left-sided breast and regional lymph node radiotherapy

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Background: Irradiation of internal mammary (IMNI) nodal volumes have demonstrated significant survival gains in high-risk axillary node positive breast cancer. There are, however, concerns that increases in irradiated volumes may offset this benefit and optimal delivery solutions are being investigated.

Purpose: A dosimetric study for comparison of intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and spot scanning proton beam therapy (PBT) for patients receiving IMNI.

Method: Axillary (1–4) and IMN volumes were contoured as per ESTRO guidelines on 10 CT datasets in patients previously treated in deep inspiratory breath-hold (DIBH). IMRT (four-field), VMAT (two 200° arcs), and PBT (anterior and 'en-face' beams) plans were created with the aim to treat the breast (40Gy [100%]) and regional nodes (36Gy [90%]) in 15 fractions.

Results: VMAT and PBT plans met all mandatory objectives compared with only 7/9 IMRT plans. PBT plans had lower mean heart dose (*0.6Gy ± 0.4* [1 SD]), left lung V17Gy (*11% ± 1.6*), and contralateral breast *(0.1Gy ± 0.1)* than IMRT (*4.4Gy ± 0.6 / 30.9% ± 3.3 / 2.7Gy ± 0.5)* and VMAT (*4.1Gy ± 0.4 / 32.1% ± 1.4 / 3.2Gy ± 0.1*) while achieving better coverage:

- *Breast PTV V38Gy: 99.1% ± 0.5* [PBT]; *94.1% ± 2.8* [IMRT]; *96.7% ± 1.7* [VMAT].
- *IMN PTV V36Gy: 99.6% ± 1.1* [PBT]; *93.2% ± 2.3* [IMRT]; *98.5% ± 1.6* [VMAT].
- *L1-L4 PTV V36Gy: 99.7% ± 0.6* [PBT]; *93.2 ± 3.2* [IMRT]; *98% ± 1.4* [VMAT].

Conclusion: This study demonstrates the dosimetric benefits of PBT over both photon modalities for IMNI. Further work investigating clinical correlation is necessary.

PTC58-0180

Does the relative effectiveness of Gafchromic EBT3 films in different proton beam qualities depend on the absorbed dose?

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Purpose: The response of Gafchromic EBT3 films depends on the beam quality of protons, often quantified by the dose average linear energy transfer (LET_d). We experimentally investigated if this relative effectiveness (RE) is, in addition, dose dependent.

Material and Methods: RE was defined as the apparent film dose divided by the delivered dose and experimentally characterized in an SOBP ranging from 3.0 to 3.5cm in depth at different dose levels. To enlarge the LET_d range, a low LET beam (nominal energy: 252.7MeV) was superimposed in two of the 1Gy iso-dose experiments (labeled 'b2′ and 'b3′). The delivered dose was simulated using GATE/Geant4 employing a validated beam model and normalized to measurements with a reference ionization chamber in the SOBP. Stacks of 5-6 films were placed in the center of a lateral 7x7cm^2 field at different depths in water. Films were calibrated at low LET_d, in the entrance plateau of a single-energy 179.2MeV proton beam.

Results: At a constant absorbed dose of 1Gy, RE decreased from 1.0 to 0.6 for LET_d from 0.8 to 14keV/μm, respectively (Fig 1). Increasing the absorbed dose from 2 to 10Gy increased the RE by 20%, whereas this increase was almost negligible (±2%) from 0.5 to 2Gy, i.e., in the linear dose regime of the films.

Conclusions: The RE is a function of beam quality and the absorbed dose level. LET quenching decreases with increasing dose, particularly for high doses.

PTC58-0211

Effect of perturbation factors and I values using multicenter calibration factor data in reference dosimetry of ion beams

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Currently, the calibration of ionization chambers for reference dosimetry is performed using cobalt 60 gamma rays, and the beam quality correction factors for the beam quality used by each user are used. Many data on the perturbation factors of various ionization chambers against cobalt 60 gamma rays have been reported using experiments and calculations, and new results have been reported due to the development of the Monte Carlo simulation. However, these results are not necessarily consistent due to differences in the Monte Carlo code and simulation system used. In recent years ICRU 90 reported new physical values such as I value and w value. Using the multicenter calibration factor data over the past 6 years by the Japanese secondary standard dosimetry laboratory, the perturbation factors with 10 types of cylindrical ionization chambers and 7 types of parallel plate ionization chambers were evaluated. Based on the results, the change of the absorbed dose was calculated including the influence of new I values by the ICRU 90. For the cylindrical ionization chambers the differences in the absorbed dose were close to IATA TRS 398 as a result, mainly due to the influence of new I values. For the parallel plate ionization chambers, the difference tended to be smaller than IAEA TRS 398 except for some ionization chamber mainly due to the evaluated perturbation factors against cobalt 60 gamma rays. To improve accuracy, further analysis and simulation should be required.

PTC58-0438

Microdosimetry with a 3D silicon on insulator (SOI) 'mushroom' detector in a low energy proton beamline for radiobiological experiments

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Introduction: The relative biological effectiveness (RBE) of protons depends on the linear energy transfer or lineal energy. Measurements of lineal energy spectra are however rarely performed in conjunction with proton radiobiological experiments due to lack of suitable high spatial resolution microdosimeters. The aim of this study was therefore to apply a novel silicon based microdosimeter to measure microdosimetric spectra in a low energy proton beam used for radiobiological experiments.

Method: A 3D silicon on insulator (SOI) "mushroom" detector with a sensitive volume array was used in a 14.8 MeV proton beam line. The depth dose distribution and multiple lineal energy spectra were measured by sequential introduction of polyamide absorbers with 16 μm thickness. The depth dose measurements were compared to measurements with an Advanced Markus ionization chamber (IC; PTW Freiburg, Germany). The dose–mean lineal energy spectra were compared to Monte Carlo simulations (MC) performed with GATE.

Results: The measured depth dose distributions with the mushroom detector and the IC were in good agreement. The dose-mean lineal energies were in relatively good agreement with MC simulations, with an expected elevation towards the Bragg peak. The measured dose-mean lineal energy converted to tissue, y_D, ranged from 7 keV/ μm without absorbers to 18 keV/μm at the Bragg peak and to a maximum of 26 keV/μm at the distal dose fall-off region.

Conclusion: The obtained lineal energy spectra indicate that the novel 3D SOI "mushroom" detector can be used to characterize radiation quality of proton beams for radiobiological experiments with low energy protons.

PTC58-0323

PMMA and silica optical fiber response to 16.5 MeV proton beams

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Introduction: Recently, many reports have indicated optical fibres as ionisation quenching free detectors. The aim of this project is to develop a fiber-optic-based dosimetry system for proton beam monitoring. The system allows for small size dosimetry with a fast dose-rate measurement. In these initial experiments, the radioluminescence (RL) generated in optical fibres exposed to proton beam irradiation is investigated as a function of proton dose rate.

Methods: Two optical fibres were compared: poly methyl methacrylate (PMMA) and silica. An Ocean Optic spectrometer was used to analyse the optical spectrum emitted through the different optical fibres. Irradiations were performed using a 16.5 MeV proton beam (GE PETtrace cyclotron) with proton beam currents ranging from 0.1 nA to 120 nA.

Results: The optical spectra differed significantly between the two fibre types. PMMA emitted light at a wavelength of 450 nm, while the silica spectrum showed two peaks; one peak at 460 nm and one at 650 nm. In the case of PMMA, the emission spectrum was observed to significantly change as irradiation continued, shown to correlate with possible photodarkening within PMMA. For the silica fibres, the intensity of both peaks was observed to increase as irradiation continued, the ratio of the two peaks were observed to be proportional to the dose-rate.

Conclusion: Spectral changes were observed in PMMA and silica optical fibres when exposed to 16.5 MeV protons. In PMMA fibres, these changes were observed to be due to photodarkening. While the ratio in silica fibre peaks were dose-rate dependent.

PTC58-0050

Ion recombination and polarity correction factor for thimble and parallel plane type ionization chambers in proton pencil beam scanning

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Accurate determination of absorbed dose to water following IAEATRS-398 formalism demand prior knowledge of ionization chamber (IC) correction factors (CF). This study investigate ion recombination (K_s) and polarity (K_{pol}) CF for three types of ICs in proton pencil beam scanning (PBS), where the dose rate is much higher than conventional photon radiotherapy.

Ionization measurement from $10\times10cm^2$ mono-energetic layer of proton energy 70.2-226.8MeV were carried out in water phantom at 2-8cm depths, using Roos-type parallel plate chamber (PPC05) and two thimble ICs (FC65PandCC13). Proton were delivered in continuous PBS mode from dedicated nozzle of an Isochronous-cyclotron based ProteusPlus. K_s were determined using two-voltage methods (150Vand300V), while K_{pol} were calculated from the ionization measured at $\pm$300V.

As the energy increases from 70.2 to 226.8 MeV, value of K_s also increases (Figure1) from 1.0070-1.0280 for FC65P and 1.0034-1.0287 for CC13. For PPC05, K_s remains nearly constant with mean(SD) of 1.0016(0.0003). All chambers showed minimal effect on biasing voltage (Figure2) with mean(SD) K_{pol} at 1.0009(0.0009), 1.0005(0.0005) and 0.9998(0.0006) for FC65P, CC13 and PPC05 respectively. K_s and K_{pol} for FC65P IC measured at variable depths and fixed depth of 2cm resulted similar value with maximum deviation of $\pm$0.588% and $\pm$0.117%.

In conclusion, K_s varies largely with energy for thimble IC and if not accounted properly can contribute an absolute dose error of up to 2.5%. The polarity effect remains minimum for all ICs. PPC05 showed least K_s value, insensitive to proton energy and can be consider as reference detector for absolute dose measurement in water.

PTC58-0329

Developing film dosimetry to benchmark dose distributions in dynamically collimated pencil beam scanning proton therapy

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Aim: Gafchromic™ EBT3 film may serve as an excellent dosimeter to benchmark highly conformal dose distributions achieved using dynamic collimation in PBS proton therapy treatments. However, special consideration must be given to properly characterize the observed LET dependence of film. This work focuses on the development of novel methods to characterize the variability in the film's response that are specific to the conditions of an intended treatment field.

Methods: A set of SOBPs were delivered using the IBA UN beamline at the Northwestern Medicine Chicago Proton Center. A film calibration with a Co-60 source at the University of Wisconsin Accredited Dosimetry Laboratory was determined and used to convert net optical density change (netΔOD) to absorbed dose to water for this project. This response was characterized to the dose-averaged LET calculated at each measurement depth using a benchmarked Monte Carlo model.

Results: The changes in the film's SOBP response were linear with increasing LET and appeared independent over the range of netΔOD changes studied. This favors the assumption that a single, well-established calibration curve can be used with LET-based correction factors to account for film saturation.

Conclusion: The dose response characteristics and the associated uncertainty has been quantified for EBT3 film dosimetry for a variety of different clinical beam qualities. Its use in quantitative 2D dosimetry in high LET proton environments is promising. However, care must be taken to consider how the context of the film's measurement relates to its calibration as it can impact the overall measurement uncertainty.

PTC58-0672

Radiochromic films in charged particle beams

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Radiochromic films have been shown to display under response to radiation containing higher–LET particles. The mechanism is thought to be the occurrence of multiple interactions within a sensitive volume of the film, which are then counted as a single interaction. While the effect can readily be measured and many groups have done so in the past a predictive algorithm allowing cross calibration in other modalities is lacking. This paper presents a theoretical treatment of the problem, provides a means to predict the amount of quenching for a given particle at a given energy. Finally, we present a comparison of measured quenching with our methodology. In earlier work from one of our group members the theoretical quenching was determined using a Monte Carlo simulation of an experiment where a stack of 26 EBT-3 films were irradiated using a SOBP treatment with 16 different energies. The quenching was measured by measuring the dose on each film and comparing this to the calculated value.

PTC58-0356

A new array detector for dose measurements in laser generated ultrashort proton beams used for radiobiology experiments

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One of the research directions at the ELI-NP research infrastructure in Romania, using 10 PW lasers, is to provide more insight regarding the biological effectiveness of the proton beams. One major problem is the in-beam dosimetry for these experiments, not in the least due to the extreme shortness of the pulses. Due to the specifics of the laser pulse, the proton beams generated by laser acceleration have a length of only a few nanoseconds, which means that measurements with ion chambers will be affected by large recombination correction factors. Measuring those recombination factors through the usual method is not an option because the laser frequency is rather low (0.1 Hz is to be achieved) and, at least in the beginning, the pulses will not be highly repeatable). Therefore, we have developed an array of four chambers, each polarised at a different voltage. The chamber array is now being tested in various charged particle fields, and the present paper shows the results obtained in a 19 MeV proton beam from the TR19 cyclotron from NIPNE, Magurele. In order to determine the distance between the chambers, FLUKA simulations were used to calculate the reciprocal influences of the four chambers. The recombination correction factor was then determined in the 19 MeV beam, first by the classical method than using the array detector and the differences between the two are presented. We can safely conclude that the array can be used with good results for the dosimetry in ultrashort pulses of proton beams.

PTC58-0317

Prompt gamma-ray imaging for real-time in vivo range/dose verification in proton and carbon ion therapy

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In vivo range verification is desirable to understand the range uncertainties, minimizing beam delivery errors during hadron therapy. The aim of this project is to develop a novel prompt gamma-ray imaging (PGI) detector prototype for the absolute and relative range verification of hadron therapy, which can be used in clinical routine. Our group is dedicated to develop a novel PGI detector based on a group of scintillator crystals (*Luteium Fine Silicate*) that coupled with silicon photomultipliers (SiPMs), see picture1. A physical tungsten collimator will be applied for the PG profile along the depth of a PMMA/water phantom. In the meantime, the proton dosimetry can be estimated by a scintillator-fibre based microprobe, see picture2, that is inserted to the phantom. The measurements from both detectors will be used for the determination of the relationship between "Bragg peak" and PG peak. We have done the preliminary test of those detectors at university of Birmingham with proton beam at 36MeV and obtained the time-of-flight information and a fall-off profile with an 8ns timing window and a 3 - 4.5MeV energy window. There are two more experiments coming in the next couple of months in Birmingham and *KVI*, Netherlands (150MeV proton beam and 90MeV/n carbon ion beam). More results can be presented by that time. The final aim of range verification is dose verification, so Monte Carlo (MC) Geant4 simulation tool has be applied for our experimental setup and Machine learning method will be applied as we build our project database.

PTC58-0571

Dosimetric effects of a cranial Ti mesh for intensity modulated proton therapy

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Purpose: Surgical titanium (Ti) meshes may be present in brain patients who receive intensity modulated proton therapy (IMPT). The purpose of this study is to quantify the dosimetric effects of a common Ti mesh.

Methods and Materials: IMPT plans were created in a solid water phantom with a Ti mesh(203mm, 203mm, 0.6mm) inserted at 0.5cm depth(Fig1). Two CTVs were located at 0.3 and 1.5cm depth below the mesh(Fig2). The TPS can take into account Ti by assigning material composition and density of Ti to the mesh. The IMPT plans were calculated with and without Ti override. Dose calculation grid and CT resolution were both 1mm. A multiple chamber array detector was used to measure the absolute 2-dimensional (2D) dose below the mesh at various depths from 0.6 to 6.7cm. Both pencil beam(PB) and Monte Carlo(MC) algorithms were used for dose calculation.

Results: For the calculated dose, the largest dose differences occurred downstream of the mesh at the distal edge of the target volume. The dose fall-off with Ti override was approximately 0.5 mm faster than the fall-off without Ti override. The differences between PB and MC were within 0.2 mm range. For the measured dose, the gamma (3%/3mm) passing rate was above 97%, and was within 2% difference for the absolute point dose.

Conclusion: Dose perturbation caused by the cranial Ti mesh for an enface beam appears small. The change of range caused by the mesh is within 1mm, which is the CT resolution and dose calculation grid limitation.

Physics: Absolute and Relative Dosimetry Poster Discussion Sessions

PTC58-0433

Range control through Prompt Gamma Spectroscopy with CeBr3 scintillators: Experimental evaluation of the spectroscopic unit in presence of He-4 beams

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Ion beam therapy could offer superior dose distributions compared to conventional therapy. However, the high dose gradients make the plans sensible to uncertainties. Among the consequences, large tumor margins are applied and sub-optimal treatment angles are chosen. Prompt Gamma Spectroscopy (PGS) has been demonstrated as an online and in-vivo absolute range monitoring technique for proton beams. This is possible by correlating the intensities of the discrete spectral lines produced by the energy-dependent nuclear inelastic interactions with the residual range of the beam. Therefore, the efficient detection of the gamma spectrum is the fundamental requirement for PGS. In this work, we investigate PGS in presence of ^{4}He beams at clinical relevant energies and intensities. We present the experimental evaluation of a spectroscopic unit based on $CeBr_3$ scintillators, which combine high energy resolution, low intrinsic activity and accurate timing. The experimental setup includes an advanced FADC/FPGA based system for high-rate digitalization. The results show the capability of the system to detect efficiently the discrete reactions over the full energy spectrum (Figure 1). We observed excellent performances in the low energy component, which open the possibility to detect discrete lines unique to metal implants, e.g. titanium. Finally, a robust statistical analysis based on the F-Test determined whether a thin metal insert was placed in the beam direction. The introduction of secondary detectors for noise reduction relaxed significantly the statistic requirements. In such a case, we require a factor 2.5 less events to converge below the 1% significance level (Figure 2).

PTC58-0442

Hadron beam time tracker for time-of-flight measurements of prompt-gamma

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Prompt gamma imaging (PGI) is nowadays a well-established technique for range control in particle therapy. However, the arrival time information of the particles needed for PGI is still affected either by accelerator related proton bunch drifts against the radio frequency in cyclotron facilities or by the irregular time microstructure of ion beams extracted in synchrotron facilities. Several solutions have been proposed to circumvent this issue, e.g. bunch monitors or hodoscopes. None of them have been capable so far to cope with the clinical high particle intensities within the full field of irradiation. We present a first clinical prototype of a hadron beam time tracker capable of detecting single particles within ion bunches (Fig. 1) with very good time resolution (Fig. 2). This prototype was able to provide time-of-flight information for the four beam species currently accelerated at clinical intensities at the Heidelberg Ion-Beam Therapy Center (HIT).

PTC58-0632

The development of a biologically-relevant pre-clinical radiotherapy dosimetry phantom

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Preclinical radiotherapy studies using small animals are an indispensable step in the pathway from in vitro experiments to clinical implementation. As radiotherapy techniques advance in the clinic it is important preclinical models evolve to keep in line with these developments. So far this includes the use of orthotopic tumor sites, small animal image-guided radiotherapy platforms that mimic clinical treatment delivery and the development of tissue equivalent phantoms.

One significant issue with preclinical radiation research is the lack of traceable standards to a primary calibration source. Without robust dosimetry, accuracy and reproducibility between studies is questionable. Our group have utilised the capability of 3D printing to produce a phantom of varying density to mimic the heterogeneous tissue densities in a mouse to create an anthropomorphic phantom which reflect the size, physiological features, tissue and bone densities of a real mouse.

Another advantage of 3D printing such phantom allows the unique incorporation of various detectors in specifically designed orientations. In doing so we demonstrate the use of Gafchromic EBT3 film and alanine pellets within the mouse phantom to perform a dosimetry audit across multiple institutions with Small Animal Radiation Research Platforms (SARRPs) to investigate the current status of preclinical radiation dosimetry. It is intended that these studies will provide a basis for preclinical studies with protons and heavier ions.

Physics: Quality Assurance and Verification

PTC58-0704

Dose replay for the Mevion HYPERSCAN proton therapy system

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Purpose: To import treatment delivery data back into Raystation TPS (RS) in order to compare with the original plan and ascertain delivery accuracy.

Method: A treatment plan was created in RS and delivered with a MEVION S250i Proton Therapy System with HYPERSCAN pencil beam scanning. Using RS's Python scripting capabilities, the delivery record was imported creating a new beam with the delivered energy layers, spot positions and MU. After a Monte Carlo dose calculation (Figure 1) a gamma comparison between treatment plan and delivered beam is possible.

Results and Conclusion: The ability to import delivery data back into the treatment planning system allows for quick analysis of the machine delivery. On its own, this will provide the ability to test for machine errors or inconsistencies, any dosimetric errors will be easily visible in a comparison between planned and delivered (Figures 2a and 2b). There is also the possibility of using this re-introduced treatment data for adaptive planning. This method of analysis, combined with regular machine QA to ensure correct output, would also allow testing of patient plans without the need to set up a water tank or phantom. This log-based QA has the potential to save significant time and would allow more facility throughput each day.

PTC58-0541

Validation of Geant4 Monte Carlo toolkit physics models for use in heavy ion therapy

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Carbon and oxygen ion therapies are highly conformal radiotherapy modalities, which deliver a therapeutic dose to a tumor while limiting damage to surrounding tissue. Such treatments are highly sensitive to positioning error due to the steep dose profile, which can result in under-dosing the tumor and/or overdosing healthy tissue.

One method for verifying the dose is to image the distribution of short-lived positron-emitting fragmentation products generated as the beam passes through the patient, using an in-beam PET system. In order to develop and validate models relating the delivered dose to the PET image, it is necessary to have a reliable Monte Carlo simulation model, which accurately reflects the physics of the interaction of ion beams with human tissue. The modelling of fragmentation involves high-energy interactions for a diverse range of nuclei and is a complex process, for which no fully validated models currently exist.

In this work, we present the result of our experimental quantification of the positron-emitting nuclei yield during carbon and oxygen ion therapy across a range of homogeneous phantoms (water, polyethylene, poly(methyl methacrylate)) using an in-beam PET scanner. Experimentally-estimated yields for each identified positron-emitting fragmentation product are compared with those predicted by a range of physics models available in the Geant4 Monte Carlo Toolkit. Our results demonstrate that overall, BIC provides the most accurate estimate of the yield and the spatial distribution of the positron-emitting fragments (see Figure 1). A comprehensive analysis of each physics model in comparison to the experimental results will be presented.

PTC58-0037

A water phantom using HV-CMOS technology for beam quality assurance, verification and dosimetry

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HV-CMOS technology is widely regarded as a promising choice for the instrumentation of future high-energy physics experiments, particularly those, which require high precision tracking. Many of the advantages of HV-CMOS technology lie in its ability to be fully monolithic and mass-produced on thin substrates at a lower cost than other pixel detector technologies. Since proton therapy beams are typically in the 60 – 230 MeV energy range and involve the use of high fluences, high precision instrumentation for hadron therapy facilities have their requirements met by HV-CMOS technology in particular the ability to be high speed, high resolution and low mass.

We will present preliminary measurements made using the FEI4 pixel sensors developed for the Inner Barrel Layer of the ATLAS experiment at CERN and the Timepix pixel sensor adapted for the tracking detector of the LHCb experiment also at CERN. These detectors were deployed in a water tank at The Rutherford Cancer Center Newport operated by Proton Partners International. This facility operates an IBA ProteusOne synchrocyclotron with beam energy 226 MeV. By scanning our detectors through a water tank into which the treatment beam is directed, measurements of the position, direction and energy loss of the treatment beam as a function of depth are performed. These measurements are being used in the design and simulation of a new HV-CMOS detector aiming for a fully 3D measurement of the dose with high accuracy when planning treatments and carrying out quality assurance and verification of the treatment beams.

PTC58-0245

3-dimensional quality assurance of isocenters in proton therapy system using motion capture cameras

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Purpose: To determine the mechanical, radiation and imaging isocenters on three-dimensional room coordinate system using motion capture cameras (MCC, Bonita B10, VICON, USA) with an in-house developed phantom named 'Eagle'.

Methods: The Eagle has two modules (Fig1). The first module is a trapezoid-shaped acryl block where four infrared markers are attached. After inserting the module into the snout-holder, motion capture cameras track infrared markers and record motion tracks while gantry rotates. By analyzing the data, the gantry mechanical isocenter can be determined in three-dimensions. The second module consisted of three blocks determines laser, radiation and kV-imaging isocenters. One block on which two films are attached with 8.0 cm separation in the y-direction can measure gantry radiation isocenter in three-dimensions from star-shots. The second block where two films are attached in 8.0 cm separation in the z-direction can measure collimator radiation isocenter. A metal bead is embedded in the middle block and it indicates the kV-imaging isocenter from CT images. A cross-hair are marked on the surface of the three blocks to align with the laser isocenter. A software automatically registers the mechanical, radiation, kV-imaging and laser isocenters was developed (Fig2).

Results: The relative difference from the laser isocenter were measured in sub-millimeter unit which are (-0.289, -0.1886, -0.0959), (0.217, 0.836, 0.009), and (0.117, 0.546, 0.103) for mechanical, radiation and kV-imaging isocenter, respectively.

Conclusion: The Eagle together with MCC is useful for accurate measurement of three isocenters in three-dimensions enhancing the efficacy of quality assurance. Funded by the National Research Foundation of Korea (2013M2A2A7043507).

PTC58-0080

Connections between rogue waves and the dynamics of poles for Nonlinear Schrödinger Equation of charged-particle beams in accelerators

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Purpose: To provide a fast way to investigate and locate the position of extreme event of a charged-particle beam in accelerators.

Methodology: A thermal wave model[1] was used to describe the dynamics of high-energy charged-particle beams. A complex beam wave function, $\Psi(\xi, \zeta)$, were used to analyze the longitudinal dynamics of particle bunches. In a circular high-energy accelerating machine, the longitudinal evolution was described by Nonlinear Schrödinger Equation(NLSE). Rogue waves are surprisingly large displacements from an equilibrium background. It is a violent event and will constitute a major risk for the beam integrity. Here, second-order rogue wave solutions[2], which was an exact rational solution to NLSE, were utilized. Locations of second-order rogue waves were correlated with the pole movement of the denominator of the solution in the complex plane, if the longitudinal extension of the beam in the exact solution was extended to the complex plane.

Results: There were two degrees of freedom by inserting two parameters, β and γ. Table 1 shows that the locations of maxima of the particle density remarkably coincide with the poles of the rogue wave solutions. Fig. 1 shows the locations with large particle density, $|\Psi|$, in one scenario.

Conclusion: By associating the zeroes of the denominator of the solution with the spatial locations of the maximum particle density, one can easily predict when beam failure occurs and optimize the design of the particle accelerator. 1) R. Fedele, et al, Phys. Lett. A 179, 407 (1993). 2) A. Ankiewicz, et al, Phys. Lett. A 375, 2782 (2011).

PTC58-0125

A fully automated method for Monte Carlo commissioning in pencil beam scanning proton therapy

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Introduction: In proton therapy, dose recomputation using an independent Monte Carlo (MC) dose engine is often suggested as an important feature of a modern quality assurance strategy. However, an accurate beam data library (BDL) must be commissioned in the MC engine to ensure fair comparisons with the treatment planning system (TPS). We propose here a method to automatically commission the fast MC code *MCsquare*, recently released open source.

Materials and Methods: The BDL of *MCsquare* requires energy-dependent parameters that describe 1) optical properties (beam divergence, spot size, correlation), 2) the energy spectrum, and 3) the number of protons per MU for absolute dose computation. This BDL is optimized from measurements acquired during TPS commissioning. Optical parameters are retrieved by fitting beam divergence and spot sizes according to the Courant-Snyder theory, considering measured spot fluences as 2D Gaussians. The mean energy and its standard deviation are optimized to reproduce measured depth dose profiles, using a Nelder-Mead method.

Finally, the obtained BDL is validated by comparing simulations of various plans (QA SOBPs) to corresponding phantom measurements. Figure 1 displays the general workflow of the method.

Results: Figure 2 shows the evaluation of several metrics after optimization of the energy spectrum, along with resulting Bragg curves. Regarding the validation, 92% of the simulated plans lead to a range difference below 1 mm while 93% show an accuracy in absolute dose better than 1%.

Conclusion: We propose an automatic way to process measurements data in order to commission MC algorithms. The method provides good results and is independent of the treatment machine.

PTC58-0427

Characterization of a high-resolution silicon diode array detector for range verification in scanning proton beam therapy

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Background: Steep dose gradients and small beam geometries associated with scanning particle beams used for radiation therapy increases the significance of precision and results in added complexity for verification of beam characteristics for quality assurance. In this study the silicon Dose Magnifying Glass (DMG) detector is characterized for range determination for the scanning proton beam at the Mayo Clinic in Rochester.

Methods: The DMG detector (figure 1) consists of a single silicon wafer with dimensions $0.5 \times 4.0 \times 51.4$ mm^3 and an array of 256 silicon diode sensitive volumes with a pitch of 200 um. The small geometry of the detector allows for high spatial resolution dose profiling and fast range determination in a single acquisition. The DMG was positioned on the central axis of the proton beam with its longest side parallel to the incident beam direction in order to measure the relative depth dose profiles. Further, the setup and alignment sensitivity of the DMG for accurate range determination was investigated using the Monte Carlo toolkit Geant4 with beam specific parameters for available energies.

Results: Bragg peak profiles for proton energies up to $\sim$100 MeV (with range in silicon up to the length of the DMG) could be resolved (figure 2) and corresponding proton range values were determined. The measured range was consistent for independent setups. Proton ranges determined in experiment and from simulation were found to agree within 1.5%. The Monte Carlo investigation showed that the measured range is robust within reasonable angular and translational setup errors.

PTC58-0379

Spectrometric characterization of out-of-field secondary neutron beams in spatially fractionated proton therapy

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The secondary neutron spectra produced by a proton beam of 172MeV maximum beam energy, and 10×10 cm^2 field size, irradiating a 60x30x30 cm^3 water phantom, were measured at the Centrum Cyklotronowe Bronowice, Krakow, PL, within the framework of a joint experimental campaign of Working Group 9 of the European Radiation Dosimetry Group (EURADOS). In this experiment, a brass proton beam collimator was used. Collimators produce spatially fractionated irradiation fields frequently used to treat bulky tumors. Results are compared to previously measured neutron spectra produced by uncollimated proton beams, under the same irradiation conditions.

The secondary neutron component produced by proton interactions with the patient and the beam delivery system is concerning because it causes unwanted dose to the patient, increasing the risk of secondary cancers. Moreover, neutrons constitute the main radiation hazard for exposed workers and members of the public. The characterization of the energy spectrum and the total neutron fluence around proton therapy accelerators is therefore of crucial importance for radioprotection purposes and shielding design. The measurement of neutrons produced in proton therapy facilities are extremely challenging due to the wide energy range and the highly pulsed time structure of the neutron field.

Spectra were acquired at four positions inside the treatment room, using two sets of Extended-Range Bonner Sphere Spectrometers, provided by the National Physics Laboratory and the Universitat Autonoma de Barcelona, and one deuterated-stilbene scintillator supplied by the University of Michigan. The methodological approaches are reviewed and preliminary results by the different systems are compared and discussed.

PTC58-0617

From in-house to commercial: Review of daily QA performance on PSI's Gantry2 and Varian ProBeam systems

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The clinical integration of the Varian ProBeam machine at Paul Scherrer Institute was finalized in July 2018. After 6 months of clinical operation, daily quality assurance results have been analyzed and compared to those of the in-house developed Gantry2, which has been in clinical operation for more than 5 years, over the same period.

Daily QA differs between the two gantries. For the ProBeam system, commercial devices are used (IBA's Sphinx/Lynx). For dose output, a Markus Chamber inside a water-equivalent RW3 block is used, whilst beam width and position are measured using a scintillating-foil-CCD-system. Finally, the range of four different energies is evaluated at the 80% point of the distal fall-off (R80) via the CCD signal of a monoenergetic proton beam passing through different positions of a RW3 wedge. In contrast, the in-house developed solution for Gantry 2 measures range using a multi-layer ionization chamber for all clinical energies (115), whereas dose output is measured with two Farmer Chambers in PMMA. Finally, beam width and position are measured using orthogonal strip chambers.

The average deviation of 0.4±0.7% for daily dose check on the ProBeam system is comparable to that of Gantry2 (-0.6±0.6%) over the same period (fig1). A similar trend applies for range, with R80 deviating on average by -0.010±0.33mm from the expected values in the ProBeam system and 0.121±0.4mm on Gantry2.

Our analysis shows that dose and range results are accurate, reproducible and comparable for both treatment units, with daily QA being performed in both Gantries within 30 minutes.

PTC58-0101

A maximum-a-posteriori EM reconstruction method based on total variation regularization for Compton camera imaging

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Dose monitoring is a key issue to improve the quality of the treatment in proton therapy. Detection of the prompt-gamma rays produced during the treatment with a Compton camera might be a solution to meet this objective. Compton camera imaging requires to reconstruct the image of the source with specific algorithms. The reference method for gamma-ray tomography is the list-mode maximum likelihood expectation maximization (LM-MLEM).

An important issue is the high level of noise in the reconstructed images. This noise increases as the image of the source gets more precise over iterations. The low number of counts and the acquisition uncertainties faced in prompt-gamma imaging suggest the use of a priori information. We recently developed a maximum-a-posteriori EM algorithm based on total variation regularization which is particularly well suited for low-dose acquisitions. Specifically designed for Poisson noise, this algorithm allows to reduce the noise uniformly in the image, as it naturally adapts to the intensity-dependent variance. Moreover, the algorithm is faster than the methods based on splitting approaches.

We simulated a box source with non-uniform intensity and camera geometry depicted in figure 1. For the reconstruction we used 20,000 detected events corresponding to the expected number of counts for the acquisition of a single spot in proton therapy (10^8 protons). Results show that the TV a priori strongly reduces the noise and facilitates the reconstruction of the prompt-gamma distribution.

PTC58-0497

Validation of GPU-accelerated Fred Monte Carlo code for proton dose recalculation in heterogeneous media

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Monte Carlo (MC) tools provide reliable dose recalculation in heterogeneous human tissues. Their application in proton therapy can improve accuracy of dose calculations performed with treatment planning system (TPS) and support Quality Assurance (QA) procedures. A GPU-accelerated proton transport code Fred MC was developed at the University of Rome (Italy) for clinical research at proton beam facilities.

A physical beam model used for patient treatment in Krakow proton center has been implemented in Fred based on measurements performed during facility TPS commissioning. The beam model was validated against measurements in water of patient QA treatment plans with MatriXX array of ionisation chambers and of depth dose profiles of spread-out bragg peaks (SOBPs) with a Markus chamber. The implemented stoichiometric calibration was validated experimentally using the MatriXX placed behind a heterogeneous head phantom.

Measurements of SOBPs of ranges from 10 to 30 cm are in agreement with Fred MC calculations (fig. 1), showing maximum dose difference up to 2%. Percentage gamma index passing rate (%GP) with 2mm/3% criteria, obtained comparing 182 simulated and measured layers of patient QA plans was 96.28(3.3)%. Dose distributions measured behind head phantom (fig. 2) are in agreement with Fred MC simulations showing 3D %GP (2mm/2%) over 99%.

The use of Fred with the validated beam model can reduce patient treatment plan verification time due to fast and reliable dose computation and can help to improve patient treatment with protons, once implemented in the clinical routine.

PTC58-0289

Comparison of Qualified Medical Physics (QMP) staffing and activities in a large US academic radiation practice with photons and protons

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UT MDACC radiation oncology is a large academic practice with approximately 20 electron linacs, 2 gamma knifes, and one four beamline proton therapy facility on main campus. The qualified medical physicists (QMPs) are responsible for the safe and accurate administration of the radiation prescription.

QMP staffing per each patient and activities can be approximated [according to table provided].

Substantial similarities exist between the staffing and services provided by photon QMPs and proton QMPs. Differences include on-site staffing, as the proton center provides services over a longer treatment day and machine testing prior to returning the treatment device to clinical use. The proton machine operations and service is a 24 hour per day, seven days per week program, while generally the photon units are maintained during a 15 hour weekday. Proton QMPs routinely work on the weekend for machine and patient treatment field related QA activities.

Patients receive safe and accurate treatments on all radiation treatment units. Similar standards of practice are used on both proton and photon units. Preemptive or preventive maintenance remains an ongoing challenge for all devices.

The specialization of physicists (and others) into photon or proton groups seems inevitable. This mimics, in part, the specialization of gamma knife and MR Linac physicists.

PTC58-0214

Slow neutron detection with a cadmium-telluride (CdTe) detector for proton therapy

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Purpose: To investigate the use of a cadmium-telluride detector (CdTe) as an absolute slow neutron detector with superior photon-to-neutron discrimination for applications in clinical proton therapy.

Methods: Four different experimental setups were measured with varied parameters from a Mevion S250 passive scatter proton therapy unit. Spectra were recorded using a 25 mm^2, 1 mm thick uncollimated X-123 CdTe spectrometer with varying distances. The detector was shielded using 5 cm thick Borated Polyethylene (BPE) sheets thus minimizing the measured direct neutron spectrum from the treatment nozzle. For comparison, and to quantify the neutron spectrum produced, each setup was simulated within Geant4-10.04.p03.

Results: For each measurement a large 95.9 keV prompt gamma-ray peak resulting from ^{113}Cd thermal neutron capture within the CdTe detector was observed. We correlated the prompt gamma-ray peak intensity to the thermal neutron fluence at the detector. For a setup of 22.4 Gy, 0-5 cm SOBP, we measured a thermal neutron fluence of 2.2×10^6 n/cm^2. A simple Geant4 simulation with added neutron model estimated the same order of magnitude for the slow neutron fluence at the detector.

Conclusion: This research demonstrates the use of a cadmium-telluride detector (CdTe) as an accurate absolute thermal neutron detector for proton therapy. Current simulations are focused on correlating the slow neutron spectrum detected from neutron capture to the entire neutron energy spectrum for different clinical proton treatment setups by using a series of polyethylene absorbers in front of the CdTe detector similar to the Bonner sphere technique.

PTC58-0220

Characteristic spectrum measured from a gadolinium contrast agent (GDCA) in proton therapy: A combined experiment and Geant4 study

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Purpose: To statistically quantify the spectrum produced from a gadolinium contrast agent (GDCA) used for a novel tumor localization method in proton therapy, and to determine the origin of the dominant characteristic X-rays produced.

Methods: We irradiated a GDCA with varying concentrations (0-10,000 ppm) with a clinical proton beam. Spectra were analyzed to assess the quantity of Gd characteristic X-rays and neutron capture prompt γ-rays. We also created a model of the system in Geant4-10.04.p03. In the noisy higher energy spectral regions, we applied Savitzky-Golay smoothing and fit the data to Gaussian functions.

Results: For a setup of 22.4 Gy, 0-5 cm SOBP, 10,000 ppm Gd concentration; a measured count of 2597 $\pm$ 227 43 keV K_α photons and 700 $\pm$ 120 49 keV K_β photons were estimated (with 25% detector dead-time). A count of 277 $\pm$ 81 181.9 keV γ-rays and 1008 $\pm$ 133 79.5 keV γ-rays were determined. These measurements, considering emission probability and detection efficiency, are consistent with neutron activation of Gd producing characteristic X-rays from internal conversion in addition to prompt γ-rays. The Geant4 model yielded prompt gamma rays on the same order of magnitude as the experiment, however the particle induced X-ray emission (PIXE) simulation model needs further investigation.

Conclusion: From experiment, the dominant origin of Gd characteristic X-rays was determined to be from neutron capture from the secondary neutrons and not from PIXE. Future work will be performed to investigate if this technique could be used to localize the tumor position after GDCA injection for proton therapy.

PTC58-0167

Range variation of therapeutic carbon beams at SAGA HIMAT

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SAGA HIMAT (Heavy Ion Medical Accelerator in Tosu) has three treatment rooms (Room A, B and C) with carbon ion radiotherapy. Rooms A and B equip two beam lines with beam wobbling irradiation method. Room C equips horizontal and vertical beam lines with scanning irradiation method. We checked the stability of dose monitor and beam range for daily QA. We analyzed range variation for 5 years from treatment start. As a result, the variation of the range has been very small in room C. On the other hand, the magnitude of the variation was periodically varied in rooms A and B. However, the variation was within 1mm. Thus it does not affect treatment.

PTC58-0325

Dosimetric QA methodology of commercially available cyclotron-based boron neutron capture therapy system suitable for clinical practice

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Purpose: This work aims to present our institutional experience-based methodology of dosimetric QA for commercially available cyclotron-based boron neutron capture therapy (BNCT) system equipped with a beryllium target.

Methods: Based on the dosimetric QA items summarized in AAPM TG-142, the dosimetric QA procedures suitable for clinical use of commercial BNCT system were arranged based on clinical dosimetric requirements for dosimetric components such as thermal and fast neutrons and gamma constituting the irradiation field.

Results: From the results of tumor dose simulation by BNCT treatment planning system SERA, surface of beam exit port (RP_{exit}), phantom surface ($RP_{surface}$), 2-cm and 6-cm depth in phantom (RP_{peak} and RP_{distal}) on beam axis were determined as reference positions for measurement of daily, monthly, and annual QA. Each QA procedure consisted of measurements of neutron fluence by gold and indium activation rate, and gamma ray measured by thermoluminescence dosimeter. Due to intricacy of the evaluation for all components, daily beam output constancy test was limited to the evaluation for the dominantly contributed thermal neutron at RP_{exit} with gold wire activation rate using smaller proton charge amount of 0.3 C. Alternatively, thermal neutron and gamma ray measurement were added as weekly QA. Monthly QA included beam quality profile constancy test, and annual QA included a beam symmetry constancy test, output calibration of proton beam current monitor, and evaluation of linearity between proton charge value and each component dose.

Conclusion: These results provide an easy and reliable QA method that can be clinically applied with dosimetric validity for BNCT.

PTC58-0154

Implementation of isocentric chair in fixed carbon-ion beamline to treat head/neck cancer at seating position: II. architecture of control software

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Multiple fixed-beamline carbon-ion fields in patient's sagittal plane provided clinical acceptable target doses with carbon-ion high dose-gradient and enhanced radio-biological effectiveness. Using 20-degree non-planar fields at the patient's transverse plane achieve better dose-sparing of organs-at-risk. To accurately position patients treated by non-coplanar fields, a compact assembling including a Stewart hexapod platform and independent 360 rotation and 3D translation mechanisms was manufactured with a treatment workflow as shown in Fig.1. This study focuses the architecture of control software (ACS) system to operate this rotary chair; a new medical auxiliary equipment for carbon-ion radiotherapy. This ACS also includes a proper coordinate translation arithmetic (CTA) to accurately perform any displacement required by used IGRT at a different coordinate with respect to the chair as shown in Fig2.a. An efficient CTA in ACS is the key to unify the chair and the IGRT within Siemens beam control/delivery system. In addition, the open platform of ACS allows fully integrating with the Siemens system that can realize a smooth operation of clinical workflow for treating patient at seating position. By typing required IGRT displacement to the ACS instead of automatic data communication, the chair with its TCS was validated to position head phantom with typical treatment fields as shown in Fig2.b. Based on the validation, the chair was approved an accurate positioner to treat patients at seating position with non-coplanar fields. It enables more beam incident angles for using couch table only in a fixed beam line.

PTC58-0284

Scanning beam range uniformity check with EDR2 film

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We performed scanning beam range uniformity checking by sandwich EDR2 film with 2cm Gammex solidwater and checkerboard(three area with 0.2mm,0.4mm and 0.6mm different thickness), irradiated the phantom by 20×20 cm^2 square homogeneous beam field of proper energy to put film at distal position, and analyzed the pattern with ImageJ after development. Reading the pixel value of different thickness on checkerboard, we found linearity function is a good fitting for the relative range evaluation. Based on the linearity fitting function, we reached two conclusions: 1. The beam range difference at different area is within 0.1mm; and 2. Thickness resolution is 0.1mm for EDR2 film.

PTC58-0417

A detection-efficiency model in list-mode reconstruction for prompt-gamma Compton imaging

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Prompt-gamma Compton imaging has been proposed for range verification in proton therapy. The inherent properties of camera architecture and the crystals themselves are sources of systematic and random errors. Therefore, normalization correction in Compton camera is necessary to obtain accurate and reliable reconstructed images and to assure proportionality between the intensity of the reconstructed image and the emitted activity. In this study, we propose a detection-efficiency model within the list-mode maximum likelihood expectation maximization (LM-MLEM) reconstruction algorithm. The system model of LM-MLEM was split into geometrical component (C_g) and crystal-level detection efficiency component (C_{de}). The C_g was calculated by performing the probability of detecting gamma photons emitted from voxels in the object space according to the geometrical configuration of our home-made Compton camera. The C_{de} was estimated from the singles of the scatterer and the absorber detectors. To evaluate the performances of the proposed method, a plane phantom filled with ^{18}F-water was applied to simulate a gamma-emitted flood source. The inhomogeneities of the reconstructed images of the plane phantom by using LM-MLEM with and without C_{de} component were analyzed and compared. In the experimental results obtained using the proposed LM-MLEM with C_{de}, it shows an average of 19.2% improvement in inhomogeneity reduction. Further impact of detection-efficiency correction on low count Compton imaging will be discussed at the conference. In our concluding discussion, the proposed approach can provide a more accurate system model for better prompt-gamma imaging quality which should be of benefit in range verification.

PTC58-0171

Feasibility study of repainting using scanning beam to improve interplay effect in pelvic region carbon ion radiotherapy

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Purpose: We are planning to start carbon-ion scanning irradiation for pelvic region. The whole pelvic motion mainly caused by breathing induces the interplay effect as much as the target motion. In order to improve this problem, we applied a repainting beam delivery. In this study, the measured dose distribution of some treatment plans for pelvic tumors were compared between no repainting plan and repainting plan using motion phantom.

Method: Two patients with pelvic region tumor were selected for this study. We made the treatment plan with two treatment field for each plan using scanning method with repainting. The number of repainting mainly used were 6 times. We measured 2D dose distribution in center of target depth orthogonal to beam axis by using 2D ionization chamber array (OCTAVIUS Detector 1500 XDR). It was mounted on a motion phantom (Dynamic platform model 008PL). The phantom motion was sinusoidal curve with 3 mm amplitude, 3-second cycle in inferior/superior direction. The dose distributions with and without phantom motion were verified by the gamma passing rates by use of gamma analysis with reference to treatment planning. The acceptance criteria were 2 %/ 2 mm for a dose difference and a distance to agreement.

Results: Decrease of gamma passing rates by motion in no repainting cases were 4.5 - 12.7%. While decrease of gamma passing rates by motion in 4-6 repainting cases were 3.5 - 9.6%.

Conclusion: Scanning irradiation with repainting can improve the deterioration of dose distribution due to target motion.

PTC58-0413

Imaging of prompt gamma emissions during proton therapy for geometric and dosimetric verification: NPTool simulation

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The Gamma Ray Imaging (GRI+) Compton camera at the University of Liverpool is investigated for its suitability for range and dose verification of Proton Therapy (PT). The verification is done by measuring the prompt gamma emissions (PG) during treatment; providing the advantage of online treatment verification [1]. The simulation will be tested against measurements at Clatterbridge Cancer Center (CCC), where 60 MeV proton beam is used for treatment of eye cancer, and is aimed to be applicable at higher proton beam energies.[2]

The PG emitted following inelastic scattering of the proton off target nuclei are in the high energy region ranging from 2 to 10 MeV. Optimisation of the GRI+ set up for the measurement of high energy gamma rays is being performed by using simulation and laboratory measurements prior to clinical measurements at the CCC.

This poster will report on the characterisation of the GRI+ Compton Camera using Monte Carlo simulation. A code written in the NPTool framework based on the Geant4 and Root packages is used. Preliminary results are presented.[3]

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PTC58-0196

Evaluating proton pencil beam scanning treatment for breast cancer patients with breast tissue expander

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Purpose: To study the feasibility of proton pencil beam scanning (PBS) treatments for breast cancer patients with breast tissue expander and to evaluate the dose calculation accuracy of the treatment planning system (TPS).

Methods: A Mentor CPX4 breast tissue expander filled with saline on top of acrylic slabs was scanned using a Siemens Somatom Definition AS Open RT CT scanner. The expander plus 1cm acrylic was contoured as target analogous to post-mastectomy chest-wall treatment. The planning goal was to deliver at least 95% of the prescription dose to 95% of the target. A three-beam-plan was optimized using Eclipse TPS with a metal port structure template constructed based on the device geometry (Fig. 1). The Hounsfield units (HU) for the metal parts were overridden to reflect measured relative proton stopping powers (RPSP). The TPS calculated doses were compared to measured Gafchromic EBT3 film doses in acrylic.

Results: The treatment plan achieved 95% prescription dose to 98.8% of the target (Fig 1). Gamma analysis (3%3mm) comparing planned and measured film doses showed better than 93.8% pass rate in acrylic target region when all three beams were delivered (Fig 2). TPS underestimate dose inhomogeneity by more than 15% distal to the metal port in chest-wall for each individual beam but improved to mostly within 5% when all three beams were delivered (Fig 2).

Conclusion: It is feasible to treat patients with tissue expanders using multiple PBS beams using a structure template with HU overridden by measured RPSP for metal port for treatment planning.

PTC58-0083

A scintillator-based range telescope for quality assurance in particle therapy

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In particle therapy, range measurements are an integral part of the daily quality assurance (QA) process. Most treatment centers use water phantoms or Multi-Layer Ionisation Chambers for the range QA. A system is under development at University College London to provide fast, robust and cost-effective range QA measurements based on a plastic scintillator range telescope. This detector would be easy to set up and allow the verification of all range steps of a typical particle therapy center within the time of delivery.

The results of proof-of-principle experiments with clinical particle beams are presented. A prototype was built at UCL and tested in multiple treatment centers across Europe with protons, Helium and Carbon ions. The range reconstruction of protons has an uncertainty of 0.15 mm, complying with clinical standards for quality assurance detectors. During a radiation damage assessment, a dose of 6,000 Gray was delivered to the range telescope, corresponding to approximately a year's worth of integrated dose. Although a reduction in the scintillator light output of a few percent was observed, there was no quantifiable impact on the range measurement itself.

PTC58-0566

Influence of long-term spot size variability on clinical dose distribution

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Purpose: An inseparable effect of long-term gantry facility operation is the variation of beam parameters, such as the size of single pencil beams. It is very important to monitor these changes and be aware how significant they are. In this work, we analyzed spot size data from daily quality assurance procedure (QA) and attempted to estimate how beam size changes could affect clinical dose distribution was made.

Methods: The analysis included spot measurements performed during daily QA over a period of three years. Spot size variability was examined based on Gaussian sigma parameters σ calculated from measured data for energies of 70, 150 and 225 MeV. At the same time in the Varian Treatment Planning System of version 13.6 four modified beam models were implemented. For these models, σ have been increased by values between 0.6 mm and 1.2 mm relative to clinical model values. Then these modified models were used to calculate dose distribution for some exemplary treatment plans. Finally, obtained dose distributions were compared with the ones computed for the clinical beam model using gamma index analysis.

Results and Conclusions: For the analyzed QA data, the maximum difference of 0.5 mm was obtained comparing σ with reference value implemented into clinical beam model, while average difference was 0.14 mm. Performed gamma index analysis showed that differences in dose distribution become clinically significant for beam models with σ increased more than 0.6 mm, especially for initial region of treatment fields.

PTC58-0375

The QA method of energy layer switching time with pencil-beam scanning technology using planer detector

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Purpose: A new design for fast layer switching (FLS) on a Sumitomo Proton Therapy System of Kaohsiung Chang Gung Memorial Hospital has been developed. For the system, the layer switching time needs to be less than 300ms for treatment a moving target; however, it is a clinical issue to understand the delivering time for the treatment plan. We present a comprehensive method for FLS of proton pencil-beams using a quality assurance (QA) tool.

Method: A daily QA detector was used for routine pencil-beam in quality checks, i.e. beam position, spot size, scanning speed, and Bragg peak with planer detector. The FLS plan has been recorded the beam-on/off time and analyzed the data with LabView. The layer switching and beam on time were verified for routine QA and evaluated for breath-hold technology. Three pencil-beams with maximum energies were delivered, i.e. 150, 190 and 230 MeV, to a 1000cm^3 target with 24, 16, and 16 energy layers incident on the planer detector. An oscilloscope's date was compared with planer data.

Results: Total beam-on time for 1000cm^3 target were measured 15.9/15.77, 11.6/11.65, and 9.2/9.17second with oscilloscope and planer detector respectively. The average layer-switching time was 0.27second.

Conclusions: These results show that the differences between oscilloscope and planer detector are less than 0.2%. The measured method with the planer detector that we introduced was successfully detected and good enough to be comparable with the oscilloscope. It has been demonstrated for checking layer-switching time routinely and evaluating clinical plans for breath-hold technology with pencil-beam in the future.

PTC58-0122

Pretreatment QA of line scanning proton treatment by Monte Carlo simulation using machine log-files

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Purpose: Monte Carlo simulation code employing machine log-files of the pencil beam line scanning nozzle (PBN) was developed and verified.

Materials and Methods: TOPAS (TOol for PArticle Simulation) was used for PBN modeling and the code was commissioned against measured beam data. To apply machine performance for each treatment plan to simulation, the treatment plan is delivered first and the log-files in the monitor system are entered as input data to simulation using mathematical relation between the spot position and the dipole magnet strength. To verify the conversion of spot positions from log-file data to dipole magnet strengths in the MC code, nine spots for three different energies at the isocenter plane were delivered and compared with Gafchromic EBT3 film. After the spot positions and monitor unit (MU) values in log-files are converted to dipole magnet strengths and particle numbers, two-dimensional (2D) dose maps are computed. Finally, 2D dose distributions are compared with treatment planning system predictions using gamma analysis (3%/3mm). The developed code was verified for two clinical cases for two different depths.

Results: The spot positions agreed with submillimeter accuracy (Fig 1). For abdomen case, gamma passing rates were 99.84%, 98.41% at 20mm and 80mm depth, respectively. For prostate case, passing rates were 99.26%, 96.63% for port 1 and passing rates were 97.17%, 97.00% for port 2 at 20mm and 120mm depth, respectively (Table 1).

Conclusions: The MC code accounting for machine performance was successfully developed. Tests for more clinical cases are ongoing and will be presented. Funded by the National Research Foundation of Korea (2013M2A2A7043507).

PTC58-0359

Implementation of integrated quality assurance procedures for scanned ion beam delivery systems: The MedAustron experience

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The purpose of this work is to report on the MedAustron experience about the implementation of an integrated quality assurance (QA) system for scanned light-ion beam therapy (LIBT) delivery systems. Dual particle LIBT systems need an efficient daily verification of the performance and trend lines in order to guarantee patient safety and maximize beam uptime and minimize QA efforts.

The QA devices used are a commercial 2D scintillator-based detector (Lynx, IBA-Dosimetry) and a 3D water equivalent plastic phantom attached to the detector (Sphinx, IBA-Dosimetry). They are precisely positioned at isocenter using image guidance with the imaging ring system. The setup is adapted to available field sizes at MedAustron. It is used daily for every fixed proton beam line (carbon ions are currently under commissioning) and allows verifying: coincidence, dose, homogeneity, ranges, spot position and sizes. The QA workflow is implemented as an end-to-end verification integrating the CT-scan, a plan generated in the TPS and exported to the OIS. The uncertainty of the system is below 0.4mm for the range and respectively below 0.7mm and 0.3mm for the absolute spot position and size. The analysis process is automatized and relevant data is saved in a QA database. The database is readout by an in-house software providing specific trendlines, statistical analysis and tolerance and action levels.

The implementation of this QA workflow allows a quicker and easier follow-up compared to a more conventional QA system (MLIC, films, water phantom) but it also induces some limitations and accuracy or precision compromises.

PTC58-0633

Fast-prompt gamma imaging for the online monitoring of the ion range in hadron therapy

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The French collaboration ClaRyS is developing fast detectors for online ion range monitoring to reduce treatment uncertainties in hadron therapy. Prompt gamma imaging (PGI), based on the detection of prompt gamma rays following nuclear reactions along the ion track, is a promising technique for the real time verification of ion range, especially when time of flight (TOF) is used to discriminate the prompt gamma rays issued from the patient from the large background of secondary radiation.

A Compton Camera prototype has been developed by CLaRyS for PGI. Using Compton kinematics, the photon emission point is reconstructed using either an iterative process, or, if the camera is synchronised with a beam-tagging hodoscope, an analytic process involving the intersection of a line and a cone. The iterative reconstruction yielded a precision of 2 mm in the Monte Carlo simulated range for a 160 MeV proton pencil beam incident on a PMMA phantom. Whilst much quicker than the iterative reconstruction, the analytic reconstruction is less precise, but may be improved using TOF with 100 ps resolution or less. This has been studied by means of a Monte Carlo simulation.

CLaRyS has recently acquired a fast photon counting Temporal camera developed by Damavan Imaging. Although originally conceived for standalone nuclear dismantling operations, the Temporal Compton camera readout will be synchronised with the readout of a beam hodoscope. The camera is undergoing characterisation to investigate its suitability to be used as an online range monitor in hadron therapy.

Results from the two studies will be presented and discussed.

PTC58-0212

Detector timing effects at clinical dose rates in Compton-camera based prompt-gamma imaging for proton radiotherapy

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Purpose: To investigate how the inclusion of detector timing affects the data quality of a Compton-camera (CC) based prompt gamma (PG) imaging system at clinical dose rates.

Methods: Using Monte Carlo, we simulated PG detection with a clinical CC for a 150 MeV proton beam incident on a tissue equivalent phantom. Primary and phantom scattered PGs that interacted with the CC were tallied (Figure 1 A, B). The PG data was post processed to model the effects of CC dead time, data acquisition timing, and "false-coincidence" events (Figure 1 C) at clinical dose rates of 2000 Monitor Units (MU)/min (minimum), 50 000 MU/min (middle), and 180 000 MU/min (maximum). We analyzed the data in terms of energy spectrum and reconstructed PG image fidelity.

Results: As dose rate increased, we observed three effects: 1) a reduction in the total number of measured events due to increased CC dead time percentage; 2) increase in "false-coincidence" events; 3) loss of distinct PG emission peaks in the energy spectrum (Figure 2 A). For two-interaction events, the minimum dose rate dataset contained 1.0E6 events with 10% false coincidence; the middle contained 4.1E5 events with 55% false coincidence, and the maximum contained 1.6E5 events with 73% false coincidence. These effects reduced image quality and increased noise (Figure 2 B, C).

Conclusion: The CC timing effects and phantom scatter degrades data quality resulting in poor image quality at clinical dose rates. These issues may be mitigated using additional data-selection and correction techniques or hardware updates.

PTC58-0151

Dose estimation from proton-induced PET images by using the ML-EM algorithm

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Objective: Positron emission tomography (PET) has been extensively studied and clinically investigated as *in vivo* dose verification method in proton therapy. However, since the obtained PET images are not directly proportional to the dose distribution, the verification is limited to indirect ways. In this study, we developed a novel method of estimating proton dose distribution from PET images by using a maximum likelihood-expectation maximization (ML-EM) algorithm based on a filtering approach.

Methods: We irradiated water with a monoenergetic and a spread-out Bragg peak (SOBP) proton beam (max 2 Gy and 3 Gy respectively) provided by synchrotron. During and after irradiation, we performed the PET measurement for 200 s by planar-type PET. Then, the ML-EM based dose estimation algorithm was applied to the 2-D PET images.

Results: Though the obtained PET images suffered from noise and artifacts, we successfully estimated the 2-D dose distribution at almost the same quality as measured activity distribution. The computation time was only 28 ms. As for the 1-D profile along beam direction, the relative error between the estimated dose and the ground truth was less than 5% at 1 σ. The difference of 50% dose fall-off position was within 1 pixel (2 mm).

Conclusion: We conclude that our proposed algorithm achieves high-accuracy and high-speed estimation of proton dose distribution from PET images. It would bring out the further potential of PET as *in vivo* dose monitor.

PTC58-0187

Improving accuracy of protoacoustic range verification using full wave reconstruction methods

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In-vivo range verification for proton therapy is required to fully exploit its potential and, in this context, ionoaoustics (based on the detection of pressure waves originating from the thermoelastic expansion of the irradiated tissues) is being developed as an alternative approach to PET or prompt-gamma techniques.

To derive the position of the Bragg peak from the detected waves, time-of-flight (TOF) methods are commonly used. However, we believe that methods that include full wave information, where the peak position is inferred from a 3D reconstruction of the deposited dose, can be superior to TOF strategies, particularly in low signal-to-noise environments. In this work we explore two different dose-map reconstruction techniques and compare them with standard TOF for a homogeneous phantom.

To simulate emission, propagation and absorption of acoustic waves we used K-Wave, a wave-propagator in the time domain based on MATLAB. We compared the time-reversal reconstruction method implemented in K-Wave (full concurrent backpropagation of the signal from all sensors), with an in-house-developed simplified backpropagation algorithm combining full wave pressure information with a straight-rays raytracing algorithm (Figure 1, Figure 2).

Full-wave dose-map reconstruction techniques show promising trends for range determination compared to TOF methods. Full backpropagation yields superior accuracy than simplified raytracing but must be combined with multi-parallel computing in order to produce timely results. Other factors influencing spatial range accuracy (number of detector positions, hydrophone frequency response, pulse shape and duration) were studied in combination with the three considered range determination methods.

PTC58-0174

Increasing workflow efficiency using treatment control system scripting interface

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Efficiency of research and quality assurance (QA) workflows is typically impeded by the rigid design of a treatment control system (TCS), which exposes the particle therapy (PT) system to the user only via pre-defined graphical user interfaces (GUIs). Use of such pre-defined GUIs results in time-consuming manual interactions and limits the range of parameters the user can tune. Vendors recently started offering research room interfaces, however, they are typically in programming language native to the vendor's control system, which is often cumbersome as clinical users are more familiar with higher-level programming languages, like Python. To address these challenges, we have developed a dedicated scripting interface within our treatment control system (C-TCS) that allows users to access the PT system using Python scripts. In non-patient modes, the scripting interface exposes to the user: all relevant treatment data (e.g. treatment plan), motion control (e.g. couch), tuning of QA parameters (e.g. T-P correction factor) and information about dose delivery. Our interface allows an automatization and customization of research and QA workflows with custom Python scripts, and even the creation of custom GUIs, leading to reduced workflow time. Additionally, the scripting interface allows users to: cross-check DICOM data transfers from the treatment planning system to the TCS, translate DICOM data into machine-specific files, monitor readbacks from the dose delivery system and compare the delivery data with prescribed data in real time. This is especially important for QA workflows within the scope of adaptive therapy, which we believe represents the future of PT.

PTC58-0057

Validation of log based fast 3D-dose verification system (LBF3D-DVS) using simplified Monte Carlo (SMC) method for daily patient specific quality assurance

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Purpose: Conventional Patient Specific Quality Assurance (PSQA) is commonly performed by using 2D ion chamber array (2D-array). This current PSQA procedure has two big drawbacks. First, set-up of the phantom and measuring of the dose are quite time consuming and labor intensive. The other is that we cannot confirm those actual dose distributions in the patient. We developed the system to check the daily dose distributions and assessed the dose calculation accuracy of the SMC.

Methods: To verify the accuracy of the system, we compared 2D dose distributions calculated by the SMC to dose distributions measured with the 2D-array for 10 real patient plans. We also compared the 3D dose distributions with those from TPS and verified the dose delivery accuracy. 2D and 3D gamma analysis were used for the verifications.

Results: The gamma passing rate were almost 100% for the 3mm/3% criteria for the 2D analysis. For the 3D dose analysis, the gamma passing rate were around 95% for the 3mm/3% criteria. The major reason of the discrepancy of the 3D analysis is due to the different dose calculation algorithm used in the LB3D-DVS (SMC) and the TPS (PBA). The calculation time of the SMC was on average 4 minutes using a windows workstation with 8 cores and 64GB memory.

Conclusion: We developed the LB3D-DVS. This system enables reasonably fast and accurate dose verification on patient images. Therefore, we believe that this system has the potential to increase the chance of patients' receiving IMPT, which requires long PSQA time.

PTC58-0589

Dosimetric evaluation of multi-layer acrylic-disk radiation sensor (ADRS) for PBS proton therapy

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In beam commissioning for Pencil Beam Scanning (PBS), Multi-Layer-Ion-Chamber (MLIC) is the universal device to measure integral depth dose (IDD) profile, but it has limitations, such as electronic circuits, small diameter of ion-chamber and high cost.

To overcome the above-identified deficiencies of the existing device, we propose an acrylic-disk radiation sensor (ADRS) and are newly fabricated with multilayer-ADRS. It is made from 20 disks and consisted of disk-inserted plates, photomultiplier tube (PMT) and data-acquisition-system (NI-DAQ). The thickness and diameter of the disk is 2mm and 15cm, respectively. When it centered on the plate was irradiated by proton, the generated signals were monitored by PC through PMT and DAQ. Detailed measurement position is flexibly changed depending on patient case by placing solid phantom between the plates. This study evaluated dosimetric characteristics of the multilayer-ADRS with regard to response dose linearity, dose rate dependence, energy dependence and IDD profile.

Irradiation with 50, 100, 200, 300, 500 and 700 cGy yielded the relative outputs of 0.5, 1.0, 2.0, 3.0, 5.1 and 7.1, respectively. When 100 cGy were delivered at rates of 100 to 600 cGy/min, the output was consistent with the standard deviation of 0.01. And the change of the output with respect to the energy was nearby to zero. When the IDD profiles measured from multilayer-ADRS and MLIC were compared, the difference was about 0.5% at the Bragg peak.

These results show Multilayer-ADRS has the advantages of high-efficiency and low-cost, and also a significant potential as a new detector for PBS measurements.

PTC58-0322

Dosimetric, imaging, and mechanical long-term stability of the first commercial compact, pencil beam, image-guided proton therapy system

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Purpose: To assess long-term machine stability of the first commercial compact pencil beam scanning image-guided proton therapy system, the Proteus®ONE (IBA, Louvain-La-Neuve, Belgium).

Methods: Dosimetric, imaging, and mechanical stability of the Proteus®ONE was determined from in-house daily quality assurance (QA) measurements performed between September 2014 and December 2018. Measurements included absolute beam output and beam characteristics (assessed via beam flatness and symmetry) acquired using a MatriXX PT ionization chamber array. Geometric accuracy of integrated oblique stereoscopic x-ray and CBCT imaging systems were tested following TG-179 recommendations. Vendor-provided machine downtime records over the assessment period were used as a machine stability metric. Annual TLD output check results were also included.

Results and Discussion: Table 1 summarizes daily dosimetric and geometric accuracy results, showing all are within tolerance limits. Annual IROC TLD checks show excellent absolute beam output constancy. Recorded overall machine uptime to date is 97.3% (range 95.2%/year – 98.8%/year), comparable to conventional linacs. Total downtime between 09/2014 and 12/2018 was 387.9 hours, i.e. 1.2% cancellation of scheduled treatments. Software-related downtime changes reflect improvement efforts made by the vendor. Increased imaging-related issues could be attributed to installation of the first CBCT system on Proteus®ONE, which coupled with the spike in 2016 downtime provided the vendor insights for future installs. Increased mechanical-related downtime was likely due to normal machine aging over time.

Conclusion: This study shows excellent long-term machine stability of the first installed Proteus®ONE system.

PTC58-0295

Multi-layer Faraday cup with a range spreader for range measurements in proton beams

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A Multi-Layer Faraday Cup (MLFC) can be used for proton beam range measurements, but below 100 MeV its accuracy is limited due to finite thickness of the copper plates. A Range Spreader (RS) in front of the MLFC is proposed to improve range measurement accuracy by broadening the energy spectrum of the beam and allowing it to spread across more plates inside the MLFC for better fitting of its profile.

Ranges of beams produced by a synchrotron were measured with and without the RS. Kapton films of various thicknesses were placed in front of the MLFC with the RS to evaluate the sensitivity of the proposed method. MLFC range measurements over a period of more than 40 days were also collected and analyzed for reproducibility.

The RS broadened the absorption peak in the MLFC allowing Gaussian fitting at 70 MeV where previously this was not possible due to the narrowness of the distribution. MLFC with the RS was able to resolve thicknesses of about 0.1 mm Kapton at 70 MeV. Average reproducibility (s. d.) of beam range for five representative energies in the 70-250 MeV energy range was found to be 0.1 mm (water equivalent).

MLFC with RS can reliably measure ranges of proton beams with energies as low as 70 MeV and detect range changes of about 0.1 mm (water equivalent). High reproducibility of MLFC measurements allows the use of this device for energy checks as part of machine QA.

PTC58-0710

Experimental validation of treatment plans generated for Mevion HYPERSCAN

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Purpose: To investigate the dosimetric impact of the Energy Selector (ES) and Adaptive Aperture (AA) which are unique to the Mevion Hyperscan proton system.

Method: Patient specific QA plans for clinical plans generated using Raystation RS6 configured for Mevion Hyperscan were delivered to a QA phantom. The analyzed plan sites include CNS, lung, GI, breast and prostate. Measured dose distributions in proximal, middle, and distal planes of the SOBP were compared with calculated results. Gamma analyses were performed to assess the results.

Results and Conclusion: For prostate where the depths of targets are largest, the measured dose distributions match calculated ones for all three planes with an average gamma passing rate (3%/3mm) of greater than 97%. For CNS where the CTV are smaller and shallow, a high gamma passing rate has also been obtained. For GI such as pancreas and liver where the PTVs are large on average and depths are intermediate, the passing results become progressively worse from the distal to proximal planes. For breast where the field size is the largest, the gamma results are generally similar to that of the GI sites with the proximal plane being the worst and the measured doses are systematically lower than calculated ones. The larger beam spots and motion of the AA at low energies of Hyperscan are not adequately modeled in Raystation RS6, resulting in over prediction of in-field dose for large field size and shallow targets.

PTC58-0564

RSP measurement of Gammex tissue phantom and anthropomorphic phantom using an x-ray flat panel detector and a scanned proton beam

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The benefit of using protons for targeted radiation therapy is well known, but the accuracy of beam delivery to the treatment area is dependent on the predicted relative stopping power (RSP) along the beam trajectory. The 3-5% error incurred during the HU-RSP calculation substantiates the advantages of using proton radiography to directly measure the patient RSP. Here, we use beam energies up to 250MeV to produce proton radiographs of phantoms with a WEPL up to 28cm. The measured RSP of a Gammex tissue phantom is compared to the calculated values from the Bethe-Bloch formula. The measured WET values of an anthropomorphic phantom are compared to WET values calculated from the x-ray digitally reconstructed radiograph (DRR).

A scanning pencil beam with energy ranging from 100MeV to 250MeV was used to generate the radiographs. The proton beam energies were controlled by the synchrotron; no energy degraders were needed. An x-ray flat panel was used to record the protons' position and residual range, allowing easy pre-treatment verification of patient positioning without specialized equipment.

The head phantom's WET was calculated in 9 locations with WET ranging from 15cm – 28cm. WET values were measured by extracting the 75% proximal dose fall off in the energy resolved dose function (ERDF) and this was compared to the WET calculated from the x-ray DRR of the same phantom. RSP values of the Gammex phantom were measured using the same method and were found to be within 4% of the values calculated from Bethe-Bloch.

PTC58-0616

Using the ALPIDE chip as a beam monitoring system with a micrometric spatial resolution

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Given the high radiobiological effectiveness of ions, the exact knowledge of the beam properties and stopping power is crucial when a hadrontherapy treatment is to be planned. The proton CT (pCT) group in Bergen, Norway, has been developing medical applications using the ALPIDE sensor, originally developed for the Inner Tracking System of the ALICE detector. The ALPIDE chip, a CMOS Monolithic Active Pixel Sensor (MAPS), has a size of $30 \times 15 \times 0.05$ mm^3, consisting of about half-million pixels, each with a size of 29.24×26.88 μm^2. Recently, the ALPIDE chip was irradiated with carbon ion beams along its longitudinal dimension (30 mm) at the Heidelberg Ion Therapy (HIT) facility in Germany. The aim of this test was to explore the capability of the chip to track an entire ion history with a micrometric spatial resolution. Additionally, a Monte Carlo simulation of the ALPIDE chip was built using the Geant4-wrapping TOPAS simulation tool. The beam energy tested was 140 MeV/u, corresponding to a range of $\sim$25 mm in silicon. Both in the experiment and in the simulation, it was possible to track the complete path of carbon histories, up to the Bragg peak region (Fig. 1–2). To account for the particles scattering outside the sensitive area of the chip ($\sim$25 μm), in the simulation a stack of up to 5 chips was used. For the future, more experiments are planned to explore the feasibility of such a setup to be used as an online silicon QA device.

PTC58-0074

Determination of proton stopping power ratio with dual-energy CT in the presence of small structures and tissue-bone-air interfaces

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Purpose: To study the accuracy of proton stopping power ratio (SPR) determination with dual-energy computed tomography (DECT) for small structures and bone-tissue-air interfaces.

Methods: Hollow cylindrical polylactic acid (PLA) plugs (3 cm diameter, 5 cm height) were 3D-printed containing either one or three septa, thicknesses $t_{septa} = 0.8$ mm, 1.6 mm, 3.2 mm and 6.4 mm. First, the cylinders were inserted into a tissue equivalent head phantom (Figure 1) and DECT scans were obtained using a Siemens SOMATOM Definition Edge CT scanner. Effective atomic number (Z_{eff}) and electron density (ρ_e) images reconstructed from the DECT were used to produce SPR-CT images of each plug. Second, independent elemental composition analysis of the PLA plastic was used to determine the Z_{eff} and ρ_e for calculating the theoretical SPR (SPR-TH) using the Bethe-Bloch equation. Finally, for each plug, a direct measurement of SPR (SPR-DM) was obtained in a clinical proton beam and compared to SPR-CT and SPR-TH.

Results: SPR-CT for PLA agreed with SPR-TH when $t_{septa} \geq 3$ mm (CT slice thicknesses of 0.5 mm, 1.0 mm, and 3.0 mm). The PLA density was found to decrease when $t_{septa} < 3$ mm. As t_{septa} (and density) decreased, the SPR-CT values also decreased, in good agreement with the behavior of SPR-DM (Figure 2).

Conclusion: The DECT-based method for calculating SPR in thin heterogeneities showed good agreement with both theoretical and directly measured SPR values. The DECT scans accurately predicted the reduction in SPR associated with decreasing density as the septa thicknesses decreased.

PTC58-0686

Proof of principle detector for fast patient quality assurance

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Standard clinical practice in particle therapy is to verify the treatment plan for each patient before the plan is delivered. This patient specific QA process normally involves repeated delivery of the treatment plan to a water or water equivalent volume, with changes to the position of a dosimeter or dosimetric array in order to measure the volumetric dose distribution. Due to the repeated delivery of each field, patient QA can be extremely time consuming. An ideal patient QA system would allow measurements at the speed of treatment delivery ie. within a few minutes.

We present measurements with a simple proof-of-concept system for fast patient QA. The system is essentially a stripped-down proton CT detector, utilising a single tracking detector developed for the PRaVDA proton CT detector coupled to a single scintillating calorimeter module adapted from the SuperNEMO high energy physics experiment. The calorimeter consists of a plastic scintillator, providing the water-equivalent medium into which the beam is delivered. By measuring the position of each particle as it enters the calorimeter it is possible to reconstruct the dose deposition of individual particles and thereby reconstruct the 3D volumetric dose deposition.

Results are presented from experiments with protons at the Birmingham University 36MeV cyclotron showing volumetric dose reconstruction at proton rates well below clinical fluences. A method for scaling this system up to a full clinical patient QA system is also described.

PTC58-0645

Measurement of modulation power using porcine lung tissue

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The modulation power (P-mod) quantifies the degradation of Bragg-peaks due to submillimeter structures in target materials. However, such structures are not visible in clinical CTs. In this work, we present our measurement of P-mod in porcine lungs and for several proton beam energies.

A box out of RW3 and Plexiglas® with a trachea connector was used to fix the lungs. Radiopaque markers were placed on the lung surfaces and evaluated using repeated CT scans. The CTs were registered using deformable registration and 3D displacement vectors were calculated. In a test which lasted 4 hours, the maximum displacement vector was 0.42 cm. Proton depth dose measurements were carried out using the "Giraffe" multi-layer ionization chamber (IBA Dosimetry GmbH, Schwarzenbruck). These measurements were simulated retrospectively using the CT images of the phantom and the Monte-Carlo dose engine of the RayStation planning system (Raysearch Labs, Stockholm). The degradation of Bragg-peaks was calculated by convolving the simulated peaks with a Gaussian function until the degradation in measured Bragg-peaks was reached. Afterwards, the additional broadening (assumed to be due to submillimeter structures) was analyzed and P-mod was calculated.

The P-mod calculated using this setup was 98 ± 39 μm which is smaller than literature values. Furthermore, Bragg-peak positions varied by -0.1 ± 1.0 mm between measured and simulated curves.

In conclusion, we isolated the native P-mod of porcine lungs from macrostructures as our phantom allowed us to CT-image the lungs in measurement conditions. The measurement also confirmed that P-mod had no significant dependence on the energy of incident protons (see fig1).

PTC58-0680

Monte Carlo evaluation of the beta+ signal in J-PET detector for hadron therapy range monitoring application

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Interactions of therapeutic proton beams with a medium cause secondary radiation, for instance back-to-back photons originating from proton induced beta+ isotopes. These can be detected using Positron Emission Tomography (PET) and related to the beam range in proton beam therapy (PBT). At the Jagiellonian University in Krakow (Poland), a prototype of a modular, digital Time-of-Flight diagnostic whole-body PET scanner (J-PET) has been installed. A single J-PET module is constructed out of thirteen 50cm long scintillator strips. Back-to-back photons produce light pulses in a strip that are propagated to the strip edges and converted to electrical signals with silicon photomultipliers read-out by fast on-board front-end electronics. J-PET modules can be freely duplicated without influencing the detector price to optimize the detected signal and to integrate the detector in the treatment room.

In the Krakow proton facility, we investigate the abundance of back-to-back photons that can be detected by various J-PET configurations and the feasibility of the detector for PBT range monitoring. Single and multi-layer J-PET setups were implemented in GATE Monte Carlo. Full simulations of a proton beam impinging on a Polymethyl methacrylate (PMMA) target positioned isocentrically inside the J-PET were performed. Accounting for detector acceptance and detection efficiency, the time-integrated signal for a triple layer dual-head configuration is 8.6*10^-5. For this setup, the difference between the true and reconstructed origin of back-to-back photon, accounting for expected detection and signal acquisition efficiency, is about 1cm (FWHM). This number provides a rough estimate of the expected Bragg peak detection resolution.

PTC58-0554

Dose quantification in carbon therapy using positron emission tomography

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Carbon therapy is a form of particle therapy which uses a beam of accelerated Carbon-12 ions to precisely deliver a therapeutic radiation dose to a target. During carbon therapy, nuclear inelastic collisions between incident ions and target nuclei produce a range of fragments along the beam path. Some of these fragments can be positron emitting fragments, which can be used as the basis for quality assurance through positron emission tomography (PET).

Quantifying the dose delivered in particle therapy from the spatial distribution of positron-emitting fragments is difficult due to the complex and differing physics processes underlying dose deposition and fragmentation. This study investigates a method for non-invasive quantification of the dose deposited by a poly-energetic Carbon-12 beam in poly(methyl methacrylate) in one dimension. The spatial distribution of each positron-emitting fragment species was observed to be linearly independent for each primary beam energy and target material. This observation forms the basis for a relationship between observed positron annihilations and the delivered dose.

A library of mono-energetic fragment profiles was produced from 10 Monte Carlo simulated mono-energetic beams with a range of primary beam energies (Figure 1 (1)). Factor analysis was performed on activity profiles obtained following the delivery of 1000 poly-energetic Carbon-12 beams, with randomised energy weighting factors. The proportional contribution of each energy was estimated (Figure 1 (2)), and the dose was subsequently estimated to within 1% of the ground truth value (Figure 2). These results provide strong evidence supporting the proposed method for dose quantification in carbon therapy.

PTC58-0348

Quantification and verification of skin dose for patients with head and neck cancer receiving intensity modulated proton therapy (IMPT)

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Acute skin reactions in patients with head and neck cancer (HNC) receiving radiotherapy is commonly observed, the severity being dose dependent. In this study, skin doses at specified locations in ten patients with HNC receiving IMPT to the bilateral neck were measured using TLDs for the verification of planned dose and for quantification of the skin dose relative to the underlying target volume (TV) prescription. IMPT plans used a SIB approach (dose range: 5600-7000 CcGE), had been optimized for TV coverage without a specific skin dose constraint, and used three fields (RAO, LAO, and PA), as shown below.

TLD powder packets were placed by a single radiation oncologist at four neck locations: R/L upper (level II) and R/L lower (level IV).

TLDs were read following established dosimetry protocol. The skin doses were found to be linearly dependent on the distance of the point of interest to the edge of the TV (d). It was found to be 100% or more of the TV dose for d $<$ 2 mm, reducing to about 90% at d=0.5 cm, and to about 70% at d=1.3 cm. TLD doses and the estimated doses from treatment plans agreed within +/- 10%, with mean of deviation being close to 1%. In conclusion, skin dose sparing relative to the underlying TV prescription was observed, but varied according to its distance from the TV and the shape of the TV. Planning strategies to further reduce IMPT skin dose without compromising TV coverage are being explored.

PTC58-0394

A study on beam-quality estimation method of irradiation field for boron neutron capture therapy using dual phantom technique

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Introduction: Research and development of various accelerator-based irradiation systems for boron neutron capture therapy (BNCT) is underway throughout the world. Before the start of treatment with BNCT, the beam quality such as relative biological effectiveness (RBE) for the fast neutrons incident to the irradiation field must be estimated. Therefore, we developed the dual phantom technique for the estimation of beam quality, especially the fast neutron component of dose. Experiments for the dual phantom technique were performed in order to confirm its effectiveness.

Methods: One phantom was made of polyethylene with natural lithium fluoride (LiF) for 30 weight percent. The other phantom was made of polyethylene with 95%-enriched lithium-6 fluoride (6LiF) for 30 weight percent. Experimental characterization of the depth dose distributions of the neutron and gamma-ray components along the central axis was performed at Heavy Water Neutron Irradiation Facility installed at Kyoto University Reactor using activation foils and thermo-luminescent dosimeters, respectively.

Results: Experiments confirmed that the thermal neutron flux and secondary gamma-ray dose rate decreased substantially however the fast neutron flux was hardly affected in the 6LiF-polyethylene phantom. It was confirmed that the dose contribution of fast neutrons is improved from approximately 10% in the LiF-polyethylene phantom, to approximately 50% in the 6LiF-polyethylene phantom.

Conclusion: It was confirmed that the dual phantom technique provided an effective method for beam-quality estimation especially the fast neutron component in BNCT. Improvement in the accuracy achieved with the proposed technique results in improved RBE estimation for biological experiments.

PTC58-0182

Continued productivity advances in the quality assurance procedures at the Shanghai Proton and Heavy Ion Center SPHIC

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Purpose: The high initial cost of particle therapy limits its widespread use. We report Quality Assurance (QA) improvements at SPHIC with special focus on efficiency gains.

Materials and Methods: SPHIC QA is continuously reviewed with the primary aim to perfect patient safety and treatment quality and ancillary aim of economical use of resources. Updated results from Failure Modes and Effects Analysis (FMEA) techniques allow for increased time intervals for some QA procedures, while other tests are introduced. Patient plans are statistically analyzed for their use of the library of available 3000 beam settings (2 ion types, each ca. 300 discrete energies, each 5 spot sizes) and beam QA is adapted to the obtained frequency distribution. QA devices are precisely positioned by the pre-programmed robotic table. About 200 automatized 'one-click' beam requests using optimized beam plans were designed. QA analysis is supported by validated in-house software and 'one-click' Excel files for data collection, processing and trending.

Results: Automated QA workflows minimize possibility for human error. Machine QA beam time is reduced by 17 hours per week and a similar amount of time for manual data analysis. Beam time reduction equates to 500k USD cost savings or 165 additional patient treatments per year. Daily QA for four treatment rooms (TR) is performed in one hour with circa 2 minutes beam in each TR.

PTC58-0190

Non-invasive beam monitoring using the LHCb VELO module at a 40 MeV proton beamline

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In proton beam therapy, knowledge of the detailed beam properties is essential to ensure effective dose delivery to the patient. In clinical practice, currently used interceptive ionisation chambers require daily calibration and suffer from slow response time.

This contribution presents a new non-invasive method for dose online monitoring. It is based on the silicon multi-strip sensor LHCb VELO (VErtex LOcator), developed originally for the LHCb experiment at CERN. The semi-circular detector geometry offers the possibility to measure beam intensity through halo measurements without interfering with the beam core.

Results from initial tests using this monitor in the 40 MeV proton beamline at the University of Birmingham, UK are shown. Synchronised with a Faraday Cup and the RF cyclotron frequency, VELO was used as an online monitor by measuring the beam current at different dose rates in the proton beam halo and this information was used as basis for 2D and 3D beam profiles along the beamline. Experimental results demonstrate the linearity, accuracy, reproducibility and sensitivity of the VELO detector and this is discussed, in comparison with beam tracking simulations. These measurements will direct the implementation of the system at the 60 MeV proton therapy beamline at the Clatterbridge Cancer Center (CCC), UK where further studies will be performed to fully exploit the potential of the VELO detector as a beam monitor for medical accelerators.

PTC58-0507

Experimental validation of complex 3D range-modulators for scanned particle therapy in water

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The fast and precise dosimetric validation of 3D or 4D dose distributions in water is critical in state-of-the art particle therapy for the validation and optimization of complex and/or moving tumor treatments as well as for the benchmarking of new treatment modalities. Nowadays, standard clinical practice involves using a set of PinPoint ionization chambers in a water phantom to assess 3D dose distributions, but due to the limited number of PinPoint chambers, a full evaluation is prohibitively time-consuming and the evaluation of 4D dose distributions is additionally limited by the integral readout of the chambers.

To mitigate these problems, a versatile water phantom, designed for multiple 2D ionization chamber array detectors (e.g. PTW 1000P and PTW 1500XDR), was developed and tested. Due to the interchangeable detector design, the system's capabilities can be either tuned for higher spatial resolution (2.5 mm chamber pitch) or a larger field size (27 * 27 cm^2), with a standard detector readout time of 10Hz (movie mode). The stepper motor controlled axial detector movement has a precision of less than 50 microns and is synchronized to the extraction cycle of the synchrotron. The water phantom was successfully used to experimentally validate the complex dose distributions produced by 3D range modulators for scanned particle therapy at the Marburg Ionenstrahl-Therapiezentrum (MIT, Germany).

PTC58-0144

A variance reduction method to speed up robustness evaluation in proton therapy

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Introduction: The robustness of proton therapy plans is typically verified by simulating multiple scenarios of treatment errors. Most commercial tools rely on worst-case scenario selection methods, which makes the comparison with previous clinical experience (based on PTV) difficult. Alternatively, random scenario selection methods do not entail any assumption on how different error types are combined and selected. However, it generally requires simulating many scenarios. We propose a variance reduction (VR) method to reduce the number of scenarios.

Methods: In the context of random scenario selection, range and setup errors are typically sampled according to their respective Gaussian probability distribution. After dose calculation, the 10% worst DVH are discarded to generate a DVH-band representing the possible dose variation with a 90% confidence interval (equivalent to PTV concept). Due to flat tails of Gaussian distributions, large errors are rarely sampled, leading to slow convergence of the DVH-band. Replacing Gaussians with uniform distributions allows for homogeneous sampling. A weighting factor is then applied to each scenario during the statistical analysis in order to compensate for the distribution differences.

Results: Robustness of a lung proton therapy plan was tested with and without VR. Both methods lead to the same DVH-band (Figure 1). For a test involving 100 scenarios, statistical noise was reduced from 0.6 Gy down to 0.3 Gy using VR (Figures 2).

Conclusion: The random scenario selection method enables a statistically sound analysis of the robustness. Faster convergence of the test was achieved using a variance reduction technique.

PTC58-0243

A supplemental technique for analysis of pre-treatment quality assurance

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Background: PSQA measurement analysis depends on generating metrics representative of calculation and measurement agreement. This work introduces a dose-plane comparison algorithm, based on a cylindrical search shape (as opposed to the ellipse-based γ-test), with search limits empirically determined from machine QA. Dose plane agreement is reported at each measured pixel as the dose difference minimum (DDM) within an empirically-established search radius: $\Delta D_{min}(r)$.

Materials and Methods: Beamlet accuracy was sampled over a 6-month period across the full deliverable field dimensions to determine a weighted radial positional accuracy at a 99.5% confidence level. DDM analysis was performed for 75 scanning-beam proton patients. Image registration shifts were tracked to monitor set-up error and to isolate the search plane radius to random beamlet deviation. Pass rate was assigned as the percentage of measurements where $<$3% dose agreement was found within the determined search distance limit.

Results: $>$99.5% of radial beamlet deviations were less than 1.0mm. The pass rate (mean +/- std. dev) saw no change between a 3%/2mm γ-test (97.7 +/- 3.2%) and a 3%/1mm $\Delta D_{min}(r)$ (97.6 +/- 3.2%).

Discussion: Spot-delivery spatial accuracy was well within 1mm based on extensive QA and delivery logs. However, as Fig. 1 highlights, the elliptical shape of the γ-test is too exclusive with a 1mm criterion. The cylindrical search shape of the new algorithm accepts all pixels with $<$3% agreement inside the search area, proposed herein as more relevant to plan quality, and also intuitively provides additional diagnostic information by reporting dose deviation magnitude per pixel.

PTC58-0225

Fractionwise verification of delivered proton dose to prostate cancer patients based on daily in-room CT imaging

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Purpose: Retrospective proton dose calculation based on a unique dataset of daily CT images to confirm our prostate patient positioning and immobilization protocol for counterbalancing interfractional motion.

Material and Methods: For 12 prostate cancer patients treated conventionally fractionated to 74GyE with double-scattered lateral or anterior oblique proton fields, daily (27-37, median 32) in-room control CTs (cCT) were acquired. Patient preparation includes a bladder-filling drink protocol, water-filled endorectal balloon insertion, bony anatomy alignment by orthogonal X-Ray imaging, and CT-based verification of prostate location via implanted fiducial markers. Fraction doses were calculated retrospectively on all manually delineated cCTs and accumulated on the planning CT by deformable image registration (DIR) in RayStation5.99. DVH parameters of iCTVs, bladder, rectum, femoral heads, rectal and bladder wall were analyzed fractionwise prior and after DIR, and values from the cumulated and planned dose distributions were compared.

Results: Fig.1 shows the fractionwise assessed DVH parameters for one exemplary patient. In total, 375 fraction doses were analyzed without finding tendencies for improving or worsening DVH parameters over treatment time. Intended target coverage, $D_{98\%}$(iCTV)$>$95%, was missed in 29 cCTs (7.7%) due to suboptimal bladder filling, endorectal balloon position or delineation variation. No overdosage was observed ($D_{2\%}$(iCTV)$<$105%). DIR led partly to notable changes of DVH parameters (Fig.1). No alarming differences existed between planned and cumulated doses (Fig.2), but significant changes ($p<0.05$, Wilcoxon signed rank test) were found for $D_{2\%}$(iCTV), V_{75Gy}(bladder) and V_{30Gy}(bladder wall).

Conclusion: Despite some suspicious fractions, the total delivered doses to prostate cancer patients are accurate with the applied positioning and immobilization protocol.

PTC58-0014

Development of a proton range-verification method using ionoacoustic waves generated from spherical metal markers

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Metal markers used for patient positioning act as a strong pressure source when irradiated with proton beams. Although most of the resulting pressure waves are confined in the marker because of the large difference in acoustic impedance, waves with the marker resonant frequency escape this confinement; the marker briefly acts as an acoustic transmitter. Using the k-Wave Matlab toolbox, we explored the possible use of this phenomenon as a range verification.

Specific high-frequency waves originating from the spherical gold marker were observed (see Figs. 1 and 2). The frequency depended on the marker diameter and was 1.62 MHz when the diameter was 2.0 mm. This agreed well with the value calculated from the wave equation with the boundary condition of zero amplitude on the sphere surface. The wave amplitude was linearly correlated with the distance between the marker and the Bragg peak. If this correlation coefficient is estimated before treatment, residual beam range at the marker can be obtained in real time from the in-situ acoustic measurement.

An experiment was designed using the fixed-field alternating gradient accelerator (FFAG) at Kyoto University, Japan. Because of the short pulse and high intensity beams of the FFAG, the magnitude of the acoustic signal may reach as high as 10 Pa. To increase the sensitivity, PZT hydrophones specialized for the measurement of spherical waves with the resonance frequency are currently under development.

PTC58-0202

Daily offline range verification of proton beams at the McLaren Proton Therapy Center using a commercial mutli-layer Faraday cup

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Objective: To study the use of a Multi-Layer Faraday Cup (MLFC) for a quick and precise daily range verification of proton beams at McLaren Proton Therapy Center.

Methods: Depth dose measurements were performed at room iso-center using a water tank and Bragg Peak ion chamber. The IBA Giraffe was used to measure the water equivalent thickness (WET) of the sample copper plates used in the MLFC. The WET measurements provided the range calibration factors for the MLFC. To establish a baseline for in-room measurements, ranges were measured using the MLFC for energies from 70 to 250 MeV in steps of 10 MeV. Daily range verification measurements are performed for five representative beam energies (70, 100, 150, 200 and 250 MeV) with the MLFC, which is permanently placed at the end of the beam line inside the accelerator vault. Data collected over a period of more than 100 days are analyzed and presented.

Results: The centroid channel number in the MLFC where the protons stop was calculated and converted to depth in water and compared to the depth of distal 80% measured in the water tank. The depths agreed to within 2 mm. The daily variation in ranges measured by the MLFC was within ±0.5 mm. The total measurement time is less than 5 minutes. Daily range variation recorded was within ±0.5mm

Conclusion: Based on the measurement results, the MLFC can be used for a daily range constancy check with submillimeter accuracy. It is a quick and simple method to perform range constancy verification on a daily basis.

PTC58-0457

Thorough dosimetric evaluation of optimization techniques with an anthropomorphic head phantom

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The Normandy proton therapy center began treating patients in July 2018, most of which were treated for brain tumors or superior head and neck with SFO-IMPT robust optimization technique. While most TPS validations are performed in homogenous media such as water or water-equivalent slabs (RW3), only few validations are performed using anthropomorphic phantoms prior to treatment. The extensiontoother localizations such head and neck/pelvis or utilization of new optimization techniques, such as MFO-IMPT, require thorough validation comparing Monte Carlo (MC) dose prediction of the TPS against measurements. In this work, a complete dosimetric evaluation is performed using an anthropomorphic head phantom (CIRS). The phantom affords measurement at various depths due to its slab-stacking system. Several regions can be differentiated, such as homogeneous brain region after passing through skull, brain/bone interface, tissue/air interface, a neck region and a neck region with titanium inserts. n. Several plans are generated for the different region optimizing a cubic volume, varying different parameters such as the technique (SFO/MFO-IMPT), the number of beams (1 or 2 with different gantry angles), the airgap between the phantom and the range shifter (from 5 to 30 cm airgap). Finalized MC dose calculations are performed with a 1x1x1 mm3 resolution for an uncertainty level of 0.5%. Measurements are performed using the phantom associated to RW3 slabs as well as either the MatriXX^{ONE} or the Lynx detector (IBA Dosimetry). Preliminary results demonstrate that acceptable passing rates are achievable for 3%/1mm when using the MatriXX^{ONE} and 5%/1mm with the Lynx.

PTC58-0303

Analytical and Monte Carlo modeling of multi-parallel slit and knife-edge slit prompt gamma cameras

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Ion-range monitoring by means of prompt gammas (PG) detection is currently investigated for hadrontherapy verification. These PG emitted during the irradiation can be detected with various systems, such as collimated and Compton cameras [1]. From a general point of view, the performances of collimated cameras are mainly determined by a compromise between spatial resolution and detector efficiency.

While collimator features have been extensively investigated in the context of nuclear imaging, no theoretical considerations have been proposed for the specific 1D collimation systems developed in the context of ion-range verification during hadrontherapy, namely Multi-Parallel Slit (MPS) [2] and Knife-Edge Slit (KES) collimators [3].

The present study proposes an analytical model of these two types of collimation for deriving the main intrinsic features of MPS and KES collimators. Monte-Carlo (MC) simulations were performed to evaluate the model and to perform comparisons between the current prototypes developed by IBA and the CLaRyS collaboration.

Unlike what can be concluded from previous studies [4,5,6], the proposed analytical model showed that both types of collimation share at first order the same features in terms of detection efficiency and spatial resolution. This result confirmed by MC simulations is followed by the comparison of the prototypes precision in PG profile fall-off retrieval. 1) Krimmer Nucl. Instr. Meth. A 2018. 2) Pinto Phys. Med Biol. 2014. 3) Smeets Phys. Med. Biol. 2012. 4) Smeets Front. In Onco. 2016. 5) Lin Rad. Phys. Chem. 2017. 6) Park Nucl. Eng. Tech. 2018

PTC58-0540

Proton range verification using contrast agents and validation of simulation codes

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Range verification techniques for proton therapy include positron-emission tomography (PET) and prompt-gamma (PG) imaging, none of which have yet acquired clinical maturity. The main challenges preventing their clinical implementation are, in case of PET, the relatively long half-lives of the isotopes of interest and the large energy needed to activate PET-decaying nuclei. In case of PG, the problems are related to the wide range of energies and high instantaneous rates of the detected photons.

We have investigated on the use of certain isotopes as contrast agents for PET and PG, increasing their activation rates and shifting the activity peaks towards the Bragg peak. For this purpose, we developed the code *ActiP*, able to calculate activation of these contrast elements, and benchmarked it against Monte Carlo code TOPAS. Preliminary results show increased PET activation at the distal part of a 100-MeV proton beam, within 1mm from the Bragg peak, using Water-18O (H_2O^{18}) as a contrast agent. In addition, a good correlation between the results obtained with *ActiP* and TOPAS was obtained (Fig. 1). Time after irradiation was considered in *ActiP* (Fig. 2) and used to evaluate usability of proposed agents in a clinical environment.

PTC58-0461

A new approach to construct side-on scatterers of Compton camera for proton range verification

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Prompt-Gamma Compton camera (PGCC) has been proposed as a promising method for proton range verification. A PGCC with side-on scatterer design is under development at our laboratory. To ensure a sufficient field of view and a good spatial resolution of the PGCC, the side-on scatterer was designed based on long thin scintillator crystals. However, the accurate position-of-interaction (POI) estimation of the detector involves the use of long thin crystals is challenging. We, therefore, propose a light-sharing neural network (LS-NN) design for constructing the side-on scatterer. In this study, we present and evaluate the application of the LS-NN design to a 3×3 crystal array of 1.8×1.8×100mm3 LYSO with partially-covered reflectors. The other array with the same size of LYSO crystals with fully-covered reflectors was constructed for comparison. The crystal arrays were readout by two SiPMs from both ends. For the LS-NN design, the 3D POIs were analyzed using the proposed learning-based NN algorithm. The center-of-gravity (COG) method was performed for the conventional POI estimation. The intrinsic POI resolutions were 8.9±2.2 (LS-NN), 17.6±4.2mm (conventional) in the lateral direction, and were 1.8±0.2mm in the beam-depth direction for both designs. The energy resolutions for the LS-NN and conventional design were 32.0%±4.0%, and 44.9%±16.4%, respectively. The comparison of flood histogram and peak-to-valley ratios for the two designs will be further discussed at the conference. It is concluded the side-on scatterer using the proposed LS-NN design can provide the better performances, which shows a great promise to the development of 3D PGCC for proton range verification.

PTC58-0667

Can we use effective depth for deformable image registration QA concurrently with AAPM recommendations?

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Aim: A common problem with the QA of deformable image registration (DIR) algorithms is the absence of ground truths for performance evaluation. Effective Depth (ED) calculations could be used to determine the range errors associated with the DIR that are relevant for dose calculations.

Methods: We compared two DIR algorithms, open-source software NiftyReg and commercial solution OnQ (Oncology Systems Ltd.), by deforming two head-and-neck CT scans to a repeated scan at the end of treatment for two different modalities: repeated CT (rCT) and image-guidance MVCT. ED Dose calculations were performed using an in-house algorithm and stoichiometric calibration curves for the relevant modalities (MVCT and kVCT). The quality of the DIR performance was assessed according to APPM TG132 recommendations.

Results: The EDs were calculated for the deformed CT and the ground truth rCT and MVCT for comparison of the percentage difference. The results show that when the DIR is within tolerance according to the APPM recommendations, the %ED error is also within 3%. When the DIR is just outside the tolerance, as observed for the MVCT, the mean %ED error is between 3-4%.

Conclusion: This work highlights the potential for ED to be used as a patient specific QA measure for DIR for the purposes of proton dose calculations, which does not require labour-intensive manual contouring on the images involved.

PTC58-0164

Application of failure mode and effects analysis to treatment data transfer in a multi-vendor proton therapy center

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Aim: This study assesses the application of Failure Mode and Effects Analysis (FMEA) to treatment data transfer of a new proton facility with a multi-vendor environment involving three major vendor components in the delivery chain (i.e., Eclipse Treatment Planning System (Varian Medical Inc., USA), MOSAIQ Record and Verify systems (Elekta AB, Sweden), and an Hitachi Probeat proton beam system (Hitachi, Japan).

Methods: FMEA was applied to review the treatment data transfer process between the three major vendors mentioned. Failure modes (FM) were identified and scored according to FMEA formalism in TG 100 report. They were then ranked according to their risk priority number (RPN) using a threshold of 125.

Results: Four out of six FM exceeded the RPN threshold of 125 with the transfer of approved treatment plan parameters identified as the most critical process (RPN=288). The corresponding failure cause with the highest RPN was the potential of plan parameters being adjusted in the R&V system after the plan has been sent to R&V. The major implications could result in the delivery of unplanned doses to the patient. Additional strategies for risk mitigation include having a computer application system to facilitate automated checking by assessing the individual databases of the systems. This is preferred to manual exporting and importing of the DICOM RT plans.

Conclusion: FMEA is useful for prospective evaluation of patient safety in proton beam radiotherapy, especially critical for facilities with multi-vendor environment; and can be applied as an effective tool to mitigate potential risks in current practices.

PTC58-0669

Can a Monte Carlo based PET be used for dose delivery verification?

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Purpose: One of the challenges of particle therapy is to ensure an accurate delivery to the patient of the planned dose, since particles are more sensitive to the medium than traditional x-ray radiation. Our purpose was to develop a Fast Monte Carlo (FMC) based algorithm to compare calculated and measured PET images as a way to verify the distribution of the delivered dose in the patient.

Methods: Production of positron emitting isotopes by carbon and proton beams was incorporated into a Fast Monte Carlo (FMC) algorithm. Isotope production cross sections for different biological and non-biological materials were compared for various beam energies using GEANT4 with physics list QSGP_BIC_AllHP. The position measurement of the positron emitting isotopes during patient treatment was simulated taking into account the motion of the isotopes in the body and the resolution of the measurement devices. Calculated and measured images were compared.

Results: For protons all isotopes are produced from the medium, while for carbon they can also be generated as beam fragments. Isotope production inaccuracies introduced by the FMC approximations are of the order of 20-30%, similar to uncertainties in theoretical cross sections. Comparison of measured and calculated position of the positron emitting isotopes for a patient receiving proton in the breast shows agreement appropriate for visual dose QA.

Conclusions: PET Isotope production has been implemented in fast Monte Carlo for use in proton and carbon therapy. The current implementation seems appropriate for QA of dose delivered during patient treatment.

PTC58-0682

Quality assurance experience for a ceiling-mounted robotic cone beam CT in a proton pencil beam scanning environment

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Purpose: Our half-gantry, pencil-beam scanning proton therapy system uses a novel ceiling-mounted robotic cone-beam CT (CBCT) for imaging guidance. CBCT is performed at 3 locations including 2 positions offset 27cm and 100cm from the radiation isocenter. Here we share some QA experience over a three-year period.

Methods: Two important aspects with offset imaging isocenter QA are: 1) to ensure the accuracy of robotic patient positioning system (PPS), and 2) to ensure imagine isocenter congruence with the radiation isocenter. Daily QA includes output, range, spot position, spot size check, end to end image acquisition and registration, PPS shifts, mechanical and safety checks. Monthly QA includes additional tests for output, spot size, spot position, range, image quality, 6DOF image registration accuracy, Winston-Lutz test for coincidence of radiation versus IGRT.

Results: PPS accuracy measured with laser tracker is within +/- 0.5 mm for rotation and translation between each isocenter. Gantry radiation isocenter is within 1.0 mm radius from mechanical isocenter. Three imaging isocenters are within 0.5 mm radius from mechanical isocenter. Imaging-radiation isocenter coincidence are within 1. 3 mm at every 30-degree gantry angle for various energies. CBCT registration uncertainty measured in the end-to-end test is within +/- 0.5 mm and +/- 0.5 degree. Beam characteristics are found to be reliable such as output (within +/- 1%), spot position (+/- 1 mm), spot size FWHM (within 10%), and range (within 1mm).

Conclusion: We have instituted QA programs to routinely monitor the system performance. Off-isocenter imaging locations present unique perspective for QA.

PTC58-0036

Independent dose calculation tool for patient specific QA in ion-beam therapy

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Background: Since 2009, about 5200 patients have been treated with proton and carbon ion beams at the Heidelberg Ion-Beam Therapy Center in Heidelberg. For every single patient treatment field, the dose is measured in a water phantom, which is part of our quality assurance (QA) concept for final plan approval. Since May 2018 we use an independent dose calculation engine (DC) for clinical routine to recalculate plans from the treatment planning system (TPS) in a water phantom. The calculation results are used as patient specific (PS) verification for treatment plans.

Methods: The DC is running on its own computer and was coded independently from the TPS system by Siemens. It relies on the pencil beam model and ray tracing in a water phantom. For commissioning, calculated DC doses and dose profiles are compared to those derived from TPS and measurements. Integrating the DC into clinical routine, a workflow was established to allow treatment plan irradiation for a few fractions prior to actual dose measurements.

Results: The agreement between DC and TPS is in mean within 0.4% and to measured data in mean within 3%. The time for medical indicated re-planning is reduced to about 1/2 day from CT acquisition to plan irradiation. Furthermore, the DC tool allows grouping PS-measurements. Room time for PS-QA was decreased by up to 10%.

Conclusions: The DC for PS-QA is a powerful tool making QA scheduling and treatment planning more efficient. Furthermore, it is a fundamental step towards adaptive treatment planning.

PTC58-0077

Automated verification plan preparation and 2D-3D gamma analysis for proton patient-specific quality assurance

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Purpose: Patient-specific quality assurance (PSQA) for pencil beam scanning proton therapy is complex and time consuming, involving multiple measurements per field. We identified PSQA steps that could be automated for a more efficient workflow.

Methods: We used the treatment planning system's (TPS) capability to support C# scripts to develop an Eclipse Application Programming Interface script to automate the preparation of the verification-phantom plan (Fig. 1). The script evaluated the gradient in the target volume of each verification field based on established criteria. A local area network (LAN) connection between our measurement equipment and shared database was established to facilitate equipment control, measurement data transfer and storage. To improve measurement data analysis, a Python script was developed to automatically perform a 2D-3D γ-index analysis between the measurement plane and the corresponding TPS in-water volume for each acquired measurement. A cohort of plans representing various disease sites was evaluated with manual and automated methods to quantify time savings.

Results: The LAN connection granted immediate access to the measurement information for analysis using an online software suite. Automated verification plan preparation reduced the task time by more than 50%, decreasing the time from 5-20 minutes per field to 1-3 minutes per field. The γ-index analysis time savings is more pronounced, being reduced by an order of magnitude. We observed an average overall PSQA time savings of 57% per patient plan (Table 1).

Conclusions: Automating routine PSQA workflow elements improves time efficiency, reduces user fatigue and focuses efforts on evaluation of key quality metrics.

PTC58-0098

Preliminary results of the longitudinal clinical trial for in-vivo treatment verification in particle therapy with the INSIDE bimodal system

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In particle therapy, an on-line treatment verification device is required to reduce the uncertainty of the actual particle range during the patient's irradiation. The final aim is to better optimize the treatment plan, improving its robustness and effectiveness both in terms of dose release to the target and sparing of surrounding healthy tissues.

The INSIDE system is an innovative bi-modal instrumentation installed at the National Center of Oncological Hadron therapy (CNAO) in Pavia (Figure 1). It monitors the particle range by collecting passive signals generated by the interaction between the primary beam and human tissues. The INSIDE system consists of an in-beam Positron Emission Tomography (PET) scanner, to detect annihilation photons coming from positron emitters, and a tracker for charged particles named Dose Profiler, to detect prompt secondary protons during carbon ion treatments. The in-beam PET has been already successfully tested on a patient affected by a lacrimal gland carcinoma.

In order to predict the performance in clinics, Monte Carlo simulations were performed on a dataset of patients that had required a re-planning due to significant morphological changes. The INSIDE system resulted able to correctly detect differences in the particle range. Hence, to assess the effectiveness and feasibility of the INSIDE system, a longitudinal clinical trial (ClinicalTrials.gov Identifier: NCT03662373) is going to start in the next months. Patients affected by four selected pathologies of Head-and-Neck and Brain districts (Figure 2) will be monitored throughout their treatment.

In this contribution, the simulation study and the preliminary results of the INSIDE clinical trial will be shown.

Physics: Quality Assurance and Verification Poster Discussion Sessions

PTC58-0285

The new ICRU report on prescribing, recording and reporting light ion beam therapy

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An ICRU report on *Prescribing, Recording and Reporting Light Ion Beam Therapy* has been submitted to the Journal of the ICRU by end of 2018. This report is the result of a longstanding collaboration between the IAEA and ICRU and has been initiated after joint meetings in Vienna, Austria (2004) and Columbus, Ohio (2006) in an attempt to standardize the reporting of light ion beam radiotherapy. It relies on concepts previously developed by the ICRU for reporting other therapies but with special emphasis on the use and reporting of RBE-weighted quantities. Such harmonization will facilitate the comparison of therapeutic results obtained with ions not only between ion beam therapy centers but also with centers using other modern forms of radiation therapy, such as proton-RT and IMRT with photon beams.

The report outlines the different biological models used for calculating RBE weighted dose for light ion beam therapy and attempts to clarify their clinical use in order to enable a common understanding of clinical practice in various facilities. It gives detailed recommendations on how light ion beam therapy should be prescribed, recorded and reported. The physical and technical background of light ion beam therapy is explained. The recommendations on dosimetry were harmonized and updated according to ICRU report 90 (Key Data for Ionizing-Radiation Dosimetry: Measurement Standards and Applications, 2016) and with the upcoming revision of IAEA's TRS-398 (Absorbed Dose Determination in External Beam Radiotherapy: An International Code of Practice for Dosimetry based on Standards of Absorbed Dose to Water, 2016).

PTC58-0354

Inter-fractional monitoring in PT with 12C ions: Results of a clinical trial exploiting the detection of charged secondary particles

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In Particle Therapy (PT) the occurrence of inter-fraction morphological changes inside the patient or the small positioning variations are currently taken into account introducing large safety factors that prevent the tumor underdosage, but also unavoidably limiting the treatment efficacy. An on-line range monitoring technology, that would allow to fully profit from the high precision achievable in the dose deposition, is still missing in clinical practice. The clinical workflow foresees a new CT scan and a treatment re-planning only if significative/macroscopic morphological changes or toxicities are observed or expected in a given treatment to avoid a large amount of dose deposition to the healthy tissues. The Dose Profiler (DP) is a scintillating fibres tracker that can be used as an online monitor of Carbon ion beams treatments at the CNAO center (Pavia, Italy) exploiting the detection of charged secondary fragments escaping from the patient. The DP capability to spot the inter-fractional changes in the dose deposition using the charged fragments emission shape as a probe has been investigated with a Monte Carlo simulation using the FLUKA software and actual CT scans of patients treated at CNAO. The proposed method has been also validated against the data taken at CNAO, where the DP is currently installed, using an inhomogeneous PMMA phantom and during the first DP clinical trial (Spring 2019). The simulation and data-taking results will be presented, with particular emphasis on the discussion of the achieved inter-fractional monitoring DP performance, evaluated from the trial preliminary outcomes.

PTC58-0374

Reconstructing the 3-D proton dose distribution from the modelled iono-acoustic wave field

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Real-time range verification during proton therapy is paramount to ensure patient safety. Here, we investigate if the iono-acoustic wave field could be used to the reconstruct the 3-D proton dose distribution.

The outward propagating acoustic wave field is generated by the local temperature increase due to the deposited proton energy. The field was modelled by convolving a 3-D Green's function, representing the impulse response of the medium, with a volume density of injection rate source, describing the expansion of the medium. We computed the field resulting from a proton pulse, as would be measured by a 30×30 2-D transducer array and reconstructed the dose through model-based inversion while assuming prior knowledge of the temporal behaviour of the proton beam.

To test our method, we modelled the acoustic wave field generated by a 100 MeV clinical proton beam in water. All beam parameters were selected such as to reflect clinical values based on an isochronous cyclotron (Table). A cross section of the original proton dose distribution is shown in the figure (top row).

The figure illustrates a snapshot of the resulting pressure field (middle row). The simulated measured wave-field had a center frequency around 30 kHz and an amplitude of approximately 55 mPa. The resulting reconstructed dose (bottom row) was similar to the original dose distribution and the error in the Bragg peak location was 3.9 mm.

Imaging the proton dose distribution from the iono-acoustic wave field is feasible, while taking the temporal profile of the proton dose distribution as prior knowledge.

PTC58-0440

Improved accuracy of prompt-gamma-based range verification system enabling validation of CT-based stopping-power prediction

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Objective: To improve the accuracy of range verification with prompt-gamma-ray imaging (PGI), enabling the validation of CT-based stopping-power prediction in patients.

Material and Methods: A PGI-slit-camera system was modified to enhance its positioning accuracy, now using a floor-based docking station. The camera position is calibrated with orthogonal X-rays and its reproducibility was validated with X-ray measurements at two different days with ten repositioning iterations each. To determine the PGI simulation accuracy, the camera position derived with the X-Ray system and PGI-based range shift determination in a PMMA phantom (measured vs. simulated PGI profiles) was correlated.

Subsequently, the PGI system was clinically applied to monitor absolute proton ranges for a 1.5Gy field during eight fractions of a hypo-fractionated prostate-cancer treatment using pencil beam scanning (Fig.1). For all monitored fractions, in-room control CT scans were acquired in treatment position, enabling PGI-based range analysis for the actual patient anatomy.

Results: The reproducibility of the camera position in beam direction was $\pm$0.55mm (1σ) over different days. A 1.1mm offset in absolute range determination was found. It can be directly identified as simulation accuracy and is corrected in subsequent clinical application. The overall PGI range measurement uncertainty of about 2mm (averaging over multiple spots for global-shift determination) is well below the range prediction uncertainty (3.5%·Range+2mm). Evaluation of the clinical slit-camera application and the verification of the applied stopping-power prediction using dual-energy CT is ongoing.

Conclusion: The accuracy of PGI-based range verification was improved to enable the verification of CT-based stopping-power prediction in patients, potentially allowing for a future reduction of currently used range uncertainties.

PTC58-0480

The use of log files for patient QA and stability tracking at the Provision CARES Proton Therapy Center

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Patient treatments using the ProNova SC360 Fixed-Beam Treatment Room at the Nashville PCPTC have been underway since October 2018. While initially treating 5 patients on the first day of operation, the clinic quickly increased the patient load to 20+ patients/day in only a few weeks. Since the beginning of clinical operation, Provision and ProNova have employed log file-based QA to establish a benchmark to assess system stability and accuracy. Beginning in early 2019, both measurement- and log file-based workflows are being used in tandem for patient-specific QA with the goal of migrating towards a more log-based approach. The SC360 beamline diagnostics allow for spot size and position mapping to isocenter, integrated range and intensity verification, and beam trajectory determination using machine learning. Data is parsed from both treatment records as well as log files to form a database comprising every clinical delivery to date (actual patients as well as QA), which is analyzed on both a per patient and treatment room basis. Metrics tracked include gamma factor, primary and backup dose counter accuracy, spot position and size stability, nominal beam trajectory and system interrupt frequency. Strategies for validating the accuracy and rationality of the log-based approach will be discussed.

PTC58-0665

The prediction of patient specific quality assurance with Monte Carlo simulations for pencil beam scanning proton therapy

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Patient-specific quality assurance (PSQA) is performed on every pencil beam scanning (PBS) field by measuring doses at two water-equivalent depths, proximal (D1) and tumor (D2), including field-specific devices. A field passes QA if its 3D gamma-index (3mm/3% with 10% dose-threshold) pass-criteria above 90%. This study aims to predict PSQA results using a TOPAS MC beam model in order to omit the measurements for the fields that MC predicts pass. MC simulations were performed for 883 PBS fields and used to predict QA outcome for analytically calculated dose distributions. A total of 96% and 98.7% among D1 and D2 pass predictions respectively were confirmed as pass by the measurements (Figure 1). However, MC exhibited low performance on correctly predicting failure fields as 47% (27 of 56) and 18% (2 of 11) for D1 and D2 respectively. The correlation coefficients between the prediction and observation were 0.32 for D1 and 0.11 for D2. The high precision but marginal correlations implied that our MC model is more effective to predict pass incidents than failure incidents. Because MC unlikely (1/883) mis-predicted D1 and D2 simultaneously, it is suggested to keep performing D2 measurements for all fields and measure D1 for fields predicted as failure by MC. In this scenario, 90% of D1 measurements are expected to be replaced by MC without compromising the risk associated from the omitted the measurements. This study experimentally confirmed that MC simulations can be used to reduce the number of QA measurements in pencil beam scanning proton therapy.

PTC58-0723

Real time patient specific quality assurance

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Real time treatment is when the patient is imaged, planned, and then treated while the patient is not moved from the treatment couch. One of the obstacles to implementation is quality assurance. While the treatment plan may be compared to an independent dose calculation before treatment to verify that the plan is of high quality, there is a challenge to confirm that the treatment machine will properly deliver the plan before treating the patient without actually treating the plan on the machine. Hitachi Works is developing Real Time PSQA to mitigate this challenge. The workflow of Real Time PSQA is shown in Figure 1. The workflow for Real Time treatment plan is also the same workflow as any new plan. The only difference is how much time is between the time of imaging and the time of treatment. The DICOM RTION file of the treatment plan is transferred to a QA computer at the time of the Radiation Oncologist and Medical Physicist approval. The plan then enters the treatment preparation process and is eventually transferred to the treatment machine's Dicom Work List Manager (WLM) and Treatment Control Station (TCS) just before treatment. The product allows verification that the same plan that was reviewed by the Radiation Oncologist is the one that is about to be treated and verification of the integrity of the translation of the treatment field into machine code before treatment. Following these two verifications the patient is then treated.

Physics: Treatment Planning

PTC58-0011

Proton beam therapy vs best photons for mediastinal Hodgkin lymphoma: Dosimetric considerations and treatment: Step by step using ILROG Guidelines

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Reducing treatment-related toxicity for Hodgkin lymphomas (HL) became primordial. We describe the practical procedure inspired by the ILROG Guidelines illustrated with the first reported case of localized HL treated with Proton therapy (PT) in Europe.

We present the case of a 24 years old female with mediastinal Bulky localized mixed cellularity classic HL whom required an Involved-Site Radiation Therapy (ISRT) after complete response (CR) after polychemotherapy. 3D-conformal-radiotherapy (3DRT) was not acceptable (high doses to breasts, heart and lungs). 1) Realization of a 4D-CT-scan to evaluate target movements and another one with gating and breath-hold technique by spirometer. 2) Delineation on both CT with help from the initial PET-CT. 3) Two dosimetric plans: one with rotational intensity modulated RT (IMRT) with a Helical Tomotherapy (HT) and one with conformational PT. 4) Comparison. 95% of PTV covered by 98% and 99% of the prescribed dose with PT and HT. PT provided better OAR sparing for lungs (mean-dose (3.7Gy vs 8.4Gy), median dose (0.002Gy vs 6.9Gy) and low dose (V5Gy = 17.8% vs 54.18%)), heart (mean-dose 2,6 vs 3.7Gy), right breast (mean-dose 2.4 vs 4,4Gy) and left breast (1.9 vs 4,6Gy). We deliver 30Gy in 15 fractions choosing PT with direct anterior field using Pencil-Beam-Scanning (PBS). 5) Treatment delivery and short-term follow-up: only grade 1 skin erythema, without dysphagia or another symptom. 6) follow-up after PT: the patient is PS 0 with metabolic CR on PET-scan. PT for mediastinal HL is promising and offers a dosimetric advantage of reducing the dose to OAR.

PTC58-0386

Hypothalamic-pituitary axis and hippocampus sparing with cranio-spinal intensity modulated proton therapy: A dosimetric and comparative analysis

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Purpose: Cranio-spinal irradiation (CSI) improves clinical outcomes at the cost of long-term neuro-endocrine and cognitive sequelae. Sparing the hippocampus and hypothalamic-pituitary axis (HPA), or "functional" CSI, with intensity modulated proton therapy (IMPT) can potentially reduce this morbidity.

Materials/Methods: Data from 10 patients with medulloblastoma and ages 3-18 years were included. Targets were delineated as per our local protocol and ACNS0331 atlas. Primary objective was CSI and boost CTV D95 $>$99% coverage with robustness. Secondary objectives included the HPA and hippocampus composite Dmean $\leq$18 Gy (RBE). Brain stem was limited to V54 $<$5cc. Statistical comparison was performed with one-way ANOVA.

Results: The mean volume intentionally spared (19.8cc) with this technique was 1.35% of the whole brain CTV volume (1476cc). The composite HPA Dmean was lower in IMPT plans (1786) compared to VMAT (2184) and TOMO (2117) plans ($p=0.053$). Both hippocampus composite Dmean were lower in IMPT plans (2100) compared to VMAT (2747) and TOMO (2720) plans ($p=0.023$). IMPT CTV D95 coverage was lower in IMPT plans (5280) compared to VMAT (5462) and TOMO (5455) plans ($p<0.001$), this slight loss of coverage was due to the addition of a brain stem constraint of V54$<$5cc with IMPT plans. There was no difference in hot spots (D2) between all 3 modalities.

Conclusions: Functional CSI can reduce HPA and hippocampus doses while simultaneously maintaining the prescribed dose to the rest of the brain. A prospective clinical trial is required to establish the safety, efficiency and toxicity profile of this novel CSI approach.

PTC58-0271

Handling of implants in proton treatment planning: Results from a European survey

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Purpose: To investigate which implants in patients that are commonly causing problems in proton treatment planning and how this is handled by different clinics.

Material and methods: A questionnaire regarding handling of implants in proton treatment planning was sent to the seven clinics in Sweden where proton treatment planning is performed, and also to the clinics in the IPACS (Italy, Poland, Austria, Czech Republic, Sweden) collaboration group. The questions concerned aspects such as handling of implants in the treatment planning system (TPS), definition of metals in the CT-curve, extended CT-scale and metal artifact reduction (MAR) methods.

Results and conclusions: Answers from the eleven clinics are summarized in Table 1. The most frequently mentioned metallic implants were dental implants, cranial implants (like titanium mesh or craniofix), spine fixation, hip implants and fiducial markers. Some clinics also mentioned that they have treated patients with implants of carbon, plastics, silicon, and bone cement. Most clinics stated that they usually avoid beams through implants (at least for larger/more dense implants) and also often increase the number of beams. Several clinics routinely override HU values of implants in the TPS, but they also pointed out problems with determination of size and composition of implants. Only one clinic reported that they routinely use Monte Carlo calculations to decide whether a metallic implant treatment plan is acceptable or not. About half of the clinics use some kind of MAR software, the rest override the HU values in artifact areas.

PTC58-0184

Evaluation of robustly optimized IMPT plans using daily CBCT scans for nasopharyngeal cancer

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Purpose: Proton therapy (PT) is challenged by anatomical variations during the treatment course. In this study, the performance of a standard robust optimization technique is evaluated for patients with nasopharyngeal cancer.

Material and Methods: PT plans using simultaneous integrated boost (68/60/50Gy) were optimized for five nasopharyngeal cancer patients, treated originally with photons, using Eclipse TPS v13.7. Planning was performed using multiple-field optimization with three beam directions, and robust optimization for CTV1 (68Gy) with 5 mm perturbations in all directions. Using the Smart Adapt tool, virtual CTs (VCTs) were obtained based on deformable image registration to the planning CT from the daily CBCTs. Doses were recalculated with the original plans in the VCTs, and plan robustness was evaluated comparing CTV1 coverage (V_{95}) and OAR doses.

Results: Throughout treatment, CTV1 coverage was acceptable ($V_{95} > 99\%$). In only one fraction for one patient, target coverage was compromised ($V_{95} = 98\%$). The maximum dose to the brainstem increased approximately 13% for 2/5 patients and 15% to the spinal cord for 3/5 patients. The mean dose to the ipsilateral parotid gland increased 15% for 2/5 patients. For two patients, a 30% volume reduction of the parotid gland was observed.

Conclusions: Target volume coverage was not significantly compromised for the patients studied. An increase in dose to the OARs during treatment was observed which might give rise to increased normal tissue toxicity. Standard robust optimization designed for rigid translation may not account sufficiently for anatomical variations during treatment course.

PTC58-0192

Pencil beam scanning and split targets: An advanced planning approach for comprehensive irradiation of bilateral head and neck cancer

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Introduction: To describe a new approach for the treatment of bilateral HEAD AND NECK cancer using PBS proton therapy.

Material and Methods: HEAD AND NECK patients with bilateral lymph node irradiation are treated at our institute using a Simultaneous Integrated Boost (SIB) technique with three dose levels (54, 60, 69Gy) and a split target approach. For the latter, the targets are first split into 3 different regions in the SI direction: Head, Neck_Left, Neck_Right (Fig. 1a). Three different beam arrangements for the three regions are then defined, with the low-risk target (PTV 54) being divided into 5 sub-targets (namely PTV_Head, PTV_Hybrid_R/L, PTV_Down_R/L), each overlapping in the SI direction by 1.5 cm in order to guarantee smooth transitions along the junction region (Fig. 1b). Using this approach, full target coverage can be achieved with 6 fields, with at least 2 fields irradiating each sub-target volume. Plan robustness has been evaluated assuming set-up perturbations of 2.25 mm along each cardinal direction.

Results: The presented technique allows an almost complete sparing of medial normal tissues and OARs in the neck region (Fig. 2) whilst being deliverable in a reasonable time thanks to the restricted number of fields. Plan robustness was comparable with previously adopted techniques (e.g. a 4-field star arrangement with all fields covering all PTV's).

Conclusions: The described approach substantially spares medial normal tissues compared to other planning techniques for bilateral head and neck cases, whilst the use of multiple fields for each sub-target volume, together with overlapping junctions, guarantees clinically acceptable plan robustness.

PTC58-0229

Development of a CT metal artifact management algorithm for the improvement of head and neck proton dose calculations

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Dental amalgams (high Z materials) are common sources of artifacts in Head and Neck (HN) images. Commercial artifact reduction techniques have been offered, but many are impractical, produce inaccurate CT images or are not clinically available, thus not being widely implemented. The goal of this work is to use CT gantry tilts to develop a HN metal artifact management algorithm and investigate its improvement in proton treatment planning. The algorithm uses two angled CT scans in order to generate a single image set with minimal artifacts posterior to the metal implants. The algorithm was evaluated (geometrical distortion and HU accuracy) using a geometrical phantom simulating a HN patient with dental fillings. The phantom was jaw shaped containing teeth structures and plugs located posteriorly. The axial and sagittal views of the phantom at the same slice location at 0° without metal, 0° with metal and 30° CT tilt with metal after the algorithm showed significant improvement after the algorithm was used to manage the artifacts in the posterior region of the phantom. The integrity of the algorithm was studied based on distortion and HU accuracy, and the average total distortion for all gantry angles in the AP, LR and Z directions was 0.17 mm, 0.12 mm and 0.14 mm, respectively. The HU measurements showed significant consistency throughout the different reconstructed images when compared to the baseline image sets. Treatment planning comparisons will be performed (proton beam range differences, gamma analysis and general plan quality) between baseline and artifact corrected image sets.

PTC58-0683

On-line dose-guidance to account for inter-fractional motion during proton therapy

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Background and purpose: Proton therapy (PT) of extra-cranial tumor sites is challenged by density changes caused by inter-fractional organ motion. In this study we investigate *on-line* dose-guided PT (DGPT) to account inter-fractional target motion, exemplified by internal motion in the pelvis.

Materials and methods: On-line DGPT involved re-calculating dose distributions with the isocenter shifted up to 15mm from the position corresponding to conventional soft-tissue based image-guided PT (IGPT). The method was applied to patient models with simulated prostate/seminal vesicle target motion of ±3, ±5 and ±10mm along the three cardinal axes. Treatment plans were created using either two lateral (gantry angles of 90°/270°) or two lateral oblique fields (gantry angles of 35°/325°). Target coverage and normal tissue doses from DGPT were compared to both soft-tissue and bony anatomy based IGPT.

Results: DGPT improved the dose distributions relative to soft-tissue based IGPT for 39 of 90 simulation scenarios using lateral fields and for 50 of 90 scenarios using lateral oblique fields. The greatest benefits of DGPT were seen for large motion, e.g. a median target coverage improvement of 13% was found for 10mm anterior motion with lateral fields. DGPT also improved the dose distribution in comparison to bony anatomy IGPT in all cases. The best strategy was often to move the fields back towards the original target position prior to the simulated target motion.

Conclusion: DGPT has the potential to better account for large inter-fractional organ motion in the pelvis than IGPT.

PTC58-0694

Incorporating linear energy transfer in intensity modulated proton therapy optimization for pediatric ependymoma patients

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The purpose of this study was to investigate the potential benefit of linear energy transfer (LET) incorporated optimization of intensity modulated proton therapy (IMPT) for pediatric ependymoma patients.

Six pediatric patients with ependymoma were included in this study. In most cases, there are critical organs locating nearby target volumes. The objective function for LET optimization includes a maximization term of LET in target volumes and a minimization term of LET in critical organs and normal tissues, in addition to conventional dose-based quadratic terms. The LET-optimized plans were compared to conventional dose-optimized plans in terms of dose, LET and their product as an approximation of biological effect.

For all six pediatric patients, the LET-optimized IMPT plans were able to achieve increased LET in tumor target and decreased LET in the critical organ, i.e., the brainstem, while mean physical doses to the brainstem were slightly elevated compared to the conventional IMPT plans. The changes to biological effect resulted from LET optimization to conventional optimization varied from patient to patient (Figure 1).

LET-based IMPT optimization provides a promising tool to exploit biological effect of protons and to improve the therapeutic ratio of proton therapy. The flexibility of redistributing LET may present opportunities to improve the current treatment for pediatric ependymoma.

PTC58-0584

Study on the LET distribution as a function of different treatment planning approaches in proton beam therapy

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The RBE value of 1.1 clinically applied in proton therapy community doesn't describe all clinical situations. In a mixed particle beam, a dose-averaged LET (LET_d) over the entire particle spectrum is a quantity to correlate to biological effect. In this work, LET_d to water calculation using the Monte Carlo (MC) in the TPS RayStation (RS v5.99.50) was benchmarked against Gate8.0/Geant4.10.3 MC simulations. The aim of this work was to set up a validated tool to evaluate LET_d distributions resulting from different optimization strategies for cases with critical beam incidences.

For the LET_d benchmarking two box-like beams of 5x5x5 cm^3 centered at a depth of 6 and 30 cm in water were optimized in RS and recalculated with Gate. Plans were generated for a paediatric skull base case in RS using different optimization strategies (Single Field Optimization (SFO) and Multiple Field Optimization (MFO)) and different number of orthogonal beams.

The LET_d calculated with RS agreed with Gate within $\pm$ 5% for all profiles (figure 1). The evaluation of LET_d-Volume Histograms within the PTV and in 0.5 cm ring structure around the PTV in the paediatric case showed the maximum LET_d value of the single-beam plan is almost double if compared to the 2-beams plan approach.

PTC58-0638

Mixed-beam approach (carbon-ion boost followed by photon intensity-modulated radiotherapy) versus photon intensity-modulated radiotherapy in high-risk prostate cancer patients (AIRC-IG14300)

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Aim: To compare dosimetry in two radiotherapy approaches for high-risk prostate cancer (PCa) treatment: carbon ion radiotherapy (CIRT) boost followed by whole-pelvis intensity modulated radiotherapy (IMRT) versus conventional IMRT. We present the preliminary analysis of a phase II randomized clinical trial (NCT02672449, clinicaltrials.gov).

Method: Three consecutive high-risk PCa patients were treated with a CIRT boost receiving 16.6 Gy[RBE] in 4 fractions (4.15 Gy[RBE]/fraction) followed by whole-pelvis IMRT of 50 Gy in 25 fractions (2 Gy/fraction). Deformable registration of the planning CTs and corresponding dose was used for plan sum. A comparative IMRT photon plan was obtained as whole-pelvis IMRT of 50Gy in 25 fractions followed by a sequential boost of 28Gy in 14 fractions (both 2 Gy/fraction). The adequate target coverage was the primary goal for plan optimization. For dosimetric comparison, CIRT boost was then re-scaled to a conventional 2-Gy/fraction scheme.

Results: The rectum volume receiving 70 Gy and 40 Gy (V_{70Gy} and V_{40Gy}) were lower in CIRT+IMRT than IMRT-only plans. Similar results were found for urinary bladder. Conversely, the IMRT-only approach allows for an almost null dose to femoral heads whereas in CIRT+IMRT plans the mean V_{40Gy} was 4.1% due to CIRT beam entrance direction.

PTC58-0666

Optimisation of position resolution for the design of a clinically relevant proton CT system

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An x-ray CT image is the primary imaging technique to plan a hadron radiotherapy treatment. This x-ray CT image requires conversion via Hounsfield units to proton stopping powers to predict the behaviour of protons in the patient. This conversion however introduces a typical uncertainty of 3% on the range of the protons and hence on the predicted position of the ionising energy deposition.

This uncertainty can be removed by measuring the proton stopping power directly through proton CT. For this, the path of each individual proton into and out of the patient must be recorded, as well as its residual energy. The PRaVDA Consortium developed a proton CT system using silicon tracking detectors for a broad incident beam of protons. Proton therapy facilities have however moved towards spot scanned systems with small diameter beams and a higher instantaneous current per unit area. This presents problems which require a redesign of the system by the OPTIma project.

This work examines adaptations of the PRaVDA silicon strip detector design for such an environment. Using simulation, the effect on the position resolution of varying the strip pitch and silicon thickness has been examined. An improvement from 100um to 80um in the lateral position accuracy is observed for 60MeV protons by reducing the silicon thickness by a third. PRaVDA used an x-u-v arrangement of silicon planes to reduce tracking ambiguities. The relative performance of x-u-v and x-y configurations have been studied in a low energy proton beam and the results compared with simulation.

PTC58-0308

The role of spot-scanning proton arc therapy in the treatment of patients with left breast cancer

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Purpose: To investigate the potential dosimetric benefit of using Spot-scanning Proton Arc (SPArc) therapy for left intact breast and chestwall radiotherapy.

Methods: Three left intact breast and three left chestwall patients were included in this retrospective study. The prescription was 50Gy in 25 fractions to the Clinical Target Volume (CTV), which included the breast/chestwall and supraclavicular, axillary, and internal mammary lymph nodes. A two-field IMPT with gradient matching technique was used due to the maximum field size limitation(20x24cm) of the compact gantry design. The SPArc plans were designed using only one partial arc. The same robustness optimization parameters were used with 3.5% range and 5mm setup uncertainties and 21 worst-case-senarios). A quantitative plan robustness analysis based on the root-mean square dose volume histogram(RMS-DVH) method and interplay effect was evaluated. Treatment delivery time was calculated simulating from a proton system with 1s energy layer switching time.

Results: Ipsilateral mean lung dose was significantly reduced from 9.75Gy(IMPT) to 6.16Gy(SPArc) [p=0.01]. Area under the RMS-DVH Curve(AUC) and interplay effect results showed similar robust target coverage in the presence of setup error and breathing induced motion. Treatment delivery time of SPArc is slightly less than two field IMPT but not statistically significant (Table 1). However, SPArc only used one isocenter, which could obviate the isocenter shift and setup time in two-field IMPT.

Conclusion: SPArc has the potential to further reduce the ipsilateral lung mean dose, compared to IMPT. SPArc may also simplify the workflow when treating large target volumes that require a 2-iso field matching technique.

PTC58-0035

Commissioning of the treatment planning system RayStation at the Heidelberg Ion-Beam Therapy Center

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The Heidelberg Ion-Beam Therapy Center (HIT) uses the Raster Scan technique for proton and carbon ions. The treatment planning system (TPS) RayStation, Raysearch Laboratories, will be integrated into the application system IONTRIS, Siemens Healthineers.

As TPS commissioning for proton and carbon ions various cases of target volumes were optimized with the clinical TPS Syngo RT Planning, Siemens Healthineers, using a Pencil Beam (PB) algorithm. Dose distributions rising from simple geometries like cubic volumes in water to complex cases like anthropomorphic Rando Alderson head phantom and double-wedge phantom were recalculated in RayStation using a PB algorithm for Carbons and Monte Carlo (MC) for Protons. RayStation dose distributions were compared with syngo TPS calculations and to measurements with a 24 Pin-Point chamber array in a water phantom and for complex geometries with the 2D array Octavius1000SRS, both PTW.

For Protons both TPS were comparable for simple geometries. The RayStation MC algorithm better describes the lateral spread of the proton beam passing a range modulator and an air gap of 20 cm. For complex geometries, including cases with lateral inhomogeneities or oblique entrance, the RayStation MC shows better agreement with the measurements. The carbon PB calculation is on the same level of precision as the Syngo TPS for all geometries.

Still based on preliminary basis data, the RayStation dose calculation yields excellent results. We are looking forward to integrating RayStation into clinical routine and making use of its powerful tools.

PTC58-0549

Lower doses to hippocampi and other OARs for skull-base meningiomas with IMPT compared to VMAT and IMRT

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Purpose: To systematically compare intensity modulated proton therapy (IMPT), volumetric modulated arc therapy (VMAT) and non-coplanar intensity modulated radiotherapy (IMRT) for treatment of skull-base meningiomas larger than 3cm based on automated treatment planning. Differences in organs at risk (OARs) sparing, with specific focus on the hippocampi, and low-dose delivery were quantified.

Materials and Methods: For twenty patients automated plan generation was used to calculate a coplanar dual arc VMAT plan, an IMRT plan with nine non-coplanar beams with optimized gantry and couch angles, and a mini-max robust optimized IMPT plan with three patient-specific selected non-coplanar beams. For all plans, the same set of constraints and prioritized objectives was used. All plans were rescaled to the same target coverage.

Results: Compared to IMRT and VMAT, IMPT improved dose conformality to the target volume (Fig.1). Consequently, large dose reductions in OARs were observed (Fig.2). With respect to IMRT, mean dose and D40% in the bilateral hippocampi were on average reduced by 41%-64% and 71%-80% for conventional and stereotactic dose prescriptions, respectively (ANOVA $p \leq 0.0004$). With IMPT, the mean dose in the normal brain and the volumes receiving 10-30 Gy were 28-55% lower (ANOVA $p \leq 0.03$) compared to IMRT. When comparing IMPT and VMAT, even larger dose differences were observed, mainly due to the coplanar beam setup in VMAT.

Conclusions: For skull-base meningiomas IMPT allows for a considerable dose reduction in the hippocampi, normal brain and other OARs compared to both IMRT and VMAT, which may lead to a clinically relevant reduction of late neurocognitive side effects.

PTC58-0056

Biological optimization and dose calculation for carbon beam scanning in the Osaka Heavy Ion Therapy Center

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Introduction: A carbon beam scanning system has been introduced in Osaka Heavy Ion Therapy Center. The aim of this study is to develop biological optimization and dose calculation for commercial based treatment planning software VQA Plan (Ver5.5.1).

Methods: An analytical pencil beam algorithm with triple gaussian was adopted as the beam model. Physical property of scanning beam is modeled by Monte Carlo results and corrected considering dose measurement results. Clinical dose is calculated by Kanai-model which is well-proven in past passive irradiation. RBE is determined as cell survival in the tumor be 10% and clinical data such as restricted dose of normal tissue can be directly used from passive irradiation experience. Clinical dose, physical dose and beam weight determined at 10% survival level are linearly scaled to prescribed dose level. Dose-averaged LET (LETd) is prepared by GEANT4.9.3 Monte Carlo code and registered as beam data. LETd was separately scored into carbon isotope contribution and other fragment contribution. Biological effects of fragments other than carbon isotopes are calculated using helium LQ parameters. LQ parameter α table of carbon was integrated into Monte Carlo simulator and dose averaged α at each depth was directly scored by simulator instead of calculating α via LETd.

Results: Dose distribution in case of SOBP 6cm and maximum depth 15cm is shown in Fig.1. RBE values in the middle of SOBP agreed with past passive results within $\pm$1.5%. Cell survival at several depth in SOBP region was measured and verified to be equal.

PTC58-0636

Penumbra-based dose limit model for IMPT auto-planning

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Purpose: To improve treatment planning workflow and quality by creating an Intensity Modulated Proton Therapy (IMPT) Penumbra Dose Limit Model (PDLM) to determine optimization objectives for auto-planning implementations.

Methods: To date, most IMPT plans are manually optimized empirically and iteratively by planners, therefore often lacking in plan quality and consistency. The PDLM consists of in-water lateral penumbrae, at 5-cm depth intervals, as well as proximal dose from each single-field-optimization (SFO) treatment field. The calculated dose gradient values were stored in Look Up Tables (LUT) to estimate dose distributions surrounding planning targets. Dose grid values in a treatment plan are replaced by prescription doses within the target, and by PDLM values for penumbra and proximal doses. DVH statistics of OARs are calculated from the PDLM doses and subsequently used for RayStation plan optimization to produce a clinical IMPT plan. All steps of PDLM-based auto-plan optimization have been implemented as RayStation scripts. The PDLM model was tested on patients receiving IMPT at our institution under an IRB approved study. PDLM-optimized treatment plans were compared to manually optimized treatment plans quality and suitability for treatment delivery.

Results: PDLM allows optimization of high-quality plans for H&N, breast, and prostate disease sites, while maintaining comparable plan robustness.

Conclusions: Using the IMPT PDLM to determine treatment planning optimization objectives can produce high quality clinically deliverable treatment plans. The PDLM objectives provide an opportunity to standardize automated treatment planning. Use of the PDLM provides an opportunity improve workflow and quality.

PTC58-0655

Method of fast Monitor Unit estimation for pencil beam scanning proton therapy

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Purpose: To develop a fast and independent IMPT plan Monitor Unit (MU) estimating algorithm for plan safety check.

Methods: The total number of MU in a PBS treatment plan increases with increases of target volume, as well as areas of target profiles in beam's eye views (BEV), and, to a lesser extent, target elongation in depth. A regression analysis formula was developed based on MUs of single-field plans optimized to treat targets with a range of areas in BEVs and elongations in depth. The data were used to fit the coefficients of the regression model, including use of range shifters, described by: $\mathbf{MU_{ESTI}} = \mathbf{Const_{range_shifter}}\ \mathbf{X}\ (\mathbf{Vol_{ESTI}}/\mathbf{Vol_{Ref}})^{0.25}\ \mathbf{X}\ (\mathbf{Area_{BEV}}/\mathbf{Area_{Ref}})^{0.5}\ \mathbf{X}\ (\mathbf{Dose_{ESTI}}/\mathbf{Dose_{Ref}})\ \mathbf{X}\ \mathbf{MU_{Ref}}$, to estimate plan MUs, where $\mathbf{Const_{range_shifter}}$ is range shifter coefficient, $\mathbf{Vol_{ESTI}}$ is plan target volume, $\mathbf{Area_{BEV}}$ is target area in BEV, and $\mathbf{Dose_{ESTI}}$ is beam dose. MU for a single 1 CGE field on $10 \times 10 \times 10$ cm^3 target at 15 cm depth in water phantom was used as $\mathbf{MU_{Ref}}$. The formula was implemented as a script in RayStation treatment planning system (TPS) and tested on PBS head and neck, breast, prostate patient plans.

Results: Excellent agreements with TPS MUs were achieved for highly-conformal treatment plans. Reduced rates of agreement were observed for less conformal ones.

Conclusions: The quick MU back-calculation algorithm is designed to allow early detection of planning errors, for example, in dose prescriptions or plan normalizations, in an automated plan review process. Tests has demonstrated that the algorithm is able to detect such errors.

PTC58-0659

3D visualization tool for IMPT planning

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Purpose: To develop a 3D visualization tool in treatment planning system (TPS) for quick warning of potential patient-machine collisions and calculating air gap for each beam spot between range shifter and skin surface.

Methods and Materials: User interface of the tool is composed of a single 3D display window, together with editable beam parameters, for testing effects of alternative beam parameters on collision avoidance and air gap reduction. Visualization Toolkit (VTK) was used for Python scripting in RayStation. The visualized objects include system components (distal aspect of the nozzle, snouts, range shifters, tabletops/inserts, and imaging system panels and tubes); plan structures; and current plan parameters (isocenter, beam angle, couch angle, snout position, and spots). A VTK module (vtkImplicitPolyDataDataDistance) computes distance between system components and patient external contour. Another VTK module (vtkOBBTree) was used for spot ray tracing and calculation of air gap values for each spot. A threshold air-gap value may be set to warn planners for exceedingly large air gap values.

Results: For a given treatment plan open in TPS, the script was able to extract treatment field parameters and construct a geometric model of the delivery system and patient outer contour in 3D view with fast rendering speed. Effects of plan parameter changes are also visualized quickly.

Conclusions: The scripting tool is integrated with the TPS to assist planners in plan optimization. The tool has been implemented and tested in the TPS and the proton therapy system at the authors' institution.

PTC58-0267

Dosimetric advantages of intensity modulated proton therapy (IMPT) over volumetric modulated arc therapy (VMAT) for locally advanced nasopharyngeal cancer

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Purpose: To perform a dosimetric comparison of IMPT and VMAT in locally advanced nasopharyngeal cancer with regard to coverage of planning target volume(PTV) and sparing of organs at risk(OARs).

Methods: A total of nine patients were included in this study. The prescribed dose was 70Gy to gross tumor volume with simultaneous integrated boost to a dose of 60Gy and 54Gy in 33fractions to high risk clinical target volume (CTV) and low risk CTV respectively. IMPT and VMAT plans were generated for each patient using same dose-volume constraints. Pencil beam scanning IMPT plans were generated with multi-field optimization (MFO) using robust optimization. The paired t test was used for all statistical comparison.

Results: All plans met all normal tissue constraints and the volume covered by 95% of the prescribed dose was comparable for both IMPT and VMAT plans. Dose reductions of $>$10Gy were observed with IMPT for parotid glands and oral cavity ($p<0.0001$ for both). The mean doses in the left parotid glands, right parotid glands and oral cavity were significantly lower for IMPT (26.0Gy, 22.1Gy, 6.7Gy respectively) than VMAT(37.2Gy, 35.0Gy. 38.6Gy respectively).

Conclusion: IMPT is a promising treatment option to reduce treatment toxicities in NPC patients. However further studies are needed to determine if the dosimetric advantages conferred by IMPT translate to improvement in clinical outcome.

PTC58-0165

Dual-energy computed tomography for proton treatment planning: How much can the range uncertainty be expected to improve?

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Purpose: The purpose of this study was to quantify the accuracy and variability of a proton range estimation based on both single- and dual-energy computed tomography (CT) measurements.

Materials and Methods: Two CT scanners were used to measure both single- and dual-energy scans of four different phantoms. The dual-energy scans were used to create stopping power maps of the phantoms. The maps were subsequently used to calculate a water-equivalent thickness (WET) that was compared against a WET calculated by a treatment planning system (TPS) using the single-energy scans. The two different WET were calculated for each tissue surrogate sample separately, and the results were compared against the properties reported by the phantom manufacturers.

Results: Overall, the dual-energy approach yielded considerably more accurate WET values with root mean square error (RMSE) of about 2%, as compared to the RMSE of about 4.5% for single-energy approach. The accuracy gains were strongly dependent on the material, with bone-like samples exhibiting the strongest improvement. There were no notable differences in the variances of the calculated WET between the single- and dual-energy approaches.

Conclusion: Using dual-energy computed tomography instead of single energy can lead to significant improvements in assessing the WET of especially bony structures. For most soft tissue types, the accuracy gain is less significant.

PTC58-0547

RBE weighted dose: A comparison between LEMI, LEMIV and the dose mean LET as a biological dose estimator

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A homogenous dose distribution is crucial for a successful therapy. The enhanced biological efficiency of protons and heavier ions shifts the focus from the physical dose, used as a measurable quantity in the quality assurance, towards the biological dose which is only clinical assessable.

The relative biological efficiency (RBE) is taken as 1.1 [1] as a practical mean for protons and lies between 1.5 and 5.5 for carbon ions [2]. The RBE is dependent upon tissue type and the energy distribution of the used therapeutical beam. The biological dose is calculated as dose weighted RBE and has the unit of Gy Equivalent (GyE). In this study the biological dose of 5 patient was recalculated using the LEMIV RBE tables and a estimation based on dose weighted LET (Linear Energy Transfer) was performed. The physical dose was used as a verification for the consistency of the input database. TRiP98 [3] the treatment planning software successfully used in the pilot project at GSI was employed for recalculation. The input energy spectra needed for biological calculation was simulated using ShieldHit[4] for carbon ions and Fluka[5,6] for protons. The patient DICOM data were converted to TRiP input format using PyTrip[7]. The other data needed as input for the calculation were matched with the one of the Marburger Ion Therapy machine (MIT). Comparison through γ-Index and DVH were performed.

PTC58-0194

Accelerated partial breast irradiation with particle could significantly spare heart, contralateral breast and lung compared to photon-based radiation treatment

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Carbon-ion treatment for breast cancer has not yet been effectively analyzed and compared with photon-based radiation treatment technique. To quantitatively analyze the dosimetric effect of particle therapy on early-stage breast cancer, we compare three different kinds of radiation treatment planning by using the RayStation treatment planning system including intensity modulated carbon-ion therapy (IMCT), intensity modulated proton therapy (IMPT), and conventional photon-based VMAT.

For ten breast cancer patients referred for early stage T1N0M0 as APBI treatment, planning for IMCT, IMPT and VMAT was generated. All plan was generated based on the same CTV with different margins for PTV (2 mm for IMCT, IMPT, 3 mm for VMAT) to secure the reliability of treatment. IMCT, IMPT plan, consisting of three (non-)coplanar beam arrangement was applied with robust optimization for PTV (2 mm iso-tropical margin for patient setup uncertainty and 3.5% for range uncertainty) and VMAT with two arc beam arrangement was generated. 30 Gy in 5 fractions was applied for IMPT, VMAT whereas 30 gray equivalents (GyE; physical dose in Gy $\times$ RBE) in 5 fractions was applied for IMCT. CTV coverage and the organs at risk as well as conformity and homogeneity indexes for PTV was calculated from dose volume histograms.

All treatment plan had fulfilled the prescription ($D_{95\%}$ for CTV $\geq$ 99%). In planning comparison among the three different modalities, IMCT achieved better homogeneity compared to IMPT, VMAT and achieved better conformity compared to IMPT. Planning results from particle therapy has showed better OARs spare effect, especially for heart, contralateral breast and lung.

PTC58-0648

IMPT with simultaneous-integrated boost substantially reduces integral dose in the treatment of low-grade glioma in comparison to VMAT

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Introduction: Radiotherapy as part of the multi-modal treatment of low-grade glioma can result in late toxicities including neurocognitive changes. Intensity-modulated radiotherapy with simultaneous-integrated boost (SIB) in combination with IMPT facilitates reduced normal-tissue dose. Purpose was to identify relevant differences between VMAT and IMPT.

Methods: 4 grade-II and 3 grade-III glioma patients (WHO-classification) were treated at MedAustron with protons (IMPT). IMPT plans were optimized using single-field integrated boosts (SFIB) [Zhu et al. RadiatOncol 2014]. All IMPT-plans were clinically applied and subsequently compared to VMAT-plans using identical clinical goals for targets and OARs. CTV1 included GTV with isotropic margin of 1.0-1.5cm adapted to anatomic barriers. CTV2 (=GTV) was defined as boost volume. Respective isotropic PTV-margins were 0.3cm. 50.4/54.0Gy in 28fx and 54.0/60.0Gy in 30fx to PTV1/2 were prescribed to grade-II and -III glioma, respectively. For protons RBE=1.1 was considered. To assess integral dose a volume called total normal-tissue volume brain (TNTVb=brain-PTVs) was generated.

Results: Median PTV1, PTV2 and TNTVb volumes were 313ccm (173-479ccm), 154ccm (42-192ccm) and 1126ccm (887-1369ccm). Dosimetric parameters for PTVs (D98%,D50%,D2%,HI,CI) and for high-prioritized OARs like brainstem, optical nerves and chiasm (D2%) were comparable for VMAT and IMPT. Exposure of other critical structures, especially contra-lateral hippocampi and temporal lobes as well as TNTVb was substantially reduced for IMPT (compare Table1).

Conclusion: Both VMAT and IMPT resulted in clinically acceptable plans. Protons bear substantial potential for CNS sparing in the low-dose region. Neurocognitive testing is part of prospective follow-up at MedAustron with planned correlation of proton-dose to long-term outcome.

PTC58-0247

Verification of performance for dose estimation for BNCT by the Monte Carlo based multi-modal treatment planning system

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A project team headed by University of Tsukuba is producing a linac-based treatment device (iBNCT) for boron neutron capture therapy (BNCT). We plan to conduct a clinical trial of BNCT using the iBNCT device in the near future. In the project, a Monte Carlo based treatment planning system (Tsukuba-Plan) as an essential device to perform the treatment is also being developed in addition to the treatment device.

At present, we are verifying performance for dose estimation of Tsukuba-Plan. Measurement data were obtained several experiments performed in the iBNCT facility. A water phantom including radiation detectors inside the phantom was located to the irradiation position of the facility, and neutron beam was irradiated to the phantom. In the experiments, distributions for thermal neutron flux and gamma-ray dose which are fundamental components of BNCT dosimetry were measured. For estimation with Tsukuba-Plan, a phantom model was constructed using CT images of the phantom, and the experiments were represented. Distributions for the dose components determined by Tsukuba-Plan were compared with the experimental values. The calculations for both of thermal neutron flux and gamma-ray dose were in good agreement within error margins with the experimental values. Estimation using the realistic head phantom was also performed, the results demonstrated Tsukuba-Plan has applicability to actual treatment planning work. Fig.1 shows two-dimensional distribution for tumor dose rate in the head phantom and DVH (b).

Based on the verification results, we confirmed that Tsukuba-Plan enables perform properly dose estimation and treatment planning for BNCT using the iBNCT device.

PTC58-0199

Validation of proton stopping power ratio determination using dual energy CT

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Purpose: To validate the proton stopping power ratio (SPR) determined using dual energy CT (DECT).

Materials and Methods: A series of inserts made of different materials were scanned with both SECT and DECT in two cylindrical phantoms of 16 cm and 32 cm diameters, respectively, on a Siemens Edge DECT scanner. The water equivalent thickness (WET) of the inserts were measured with a multiple layer ion chamber (MLIC). The SPR of the inserts were then calculated using four different techniques: elemental composition of the inserts, MLIC measurement, HU/SPR calibration with SECT, and electron density/effective atomic number (ρ/Z) maps derived using DECT. An anthropomorphic phantom of thorax and pelvis sections was then scanned with SECT and DECT. WET of the phantom was calculated using SPR determined from SECT and DECT, and measured using MLIC.

Results: The measurements with MLIC and calculated SPRs based on composition agreed within 1.5%. The agreement between CT and calculated SPR for adipose, breast, solid water, water, and liver were within 1.5% for both SECT and DECT. However, for inner bone, bone, PMMA, and cortical bones, the RSP determined using DECT and calculated SPR agreed within 3%, whereas the difference ranged between 5% and 12% for SECT. For the phantom measurement, largest difference between SPR determined using SECT and DECT occurred in the bone area, and the WET calculated using DECT agrees better with MLIC measurement compared to SECT.

Conclusion: SPR determination using DECT could reduce both SPR and HU uncertainties.

PTC58-0643

Multi-field optimization intensity modulated proton therapy for nasopharyngeal carcinoma: A dosimetry comparison study in two sets of three-angle beam arrangement

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The aim of this study was to compare two different sets of beam arrangements in a multi-field optimization intensity-modulated proton therapy (MFO-IMPT) plan for nasopharyngeal carcinoma (NPC).

Ten patients with NPC retrospectively randomized selected from October 2016 to August 2018 in our institution were studied. The MFO-IMPT plans were optimized by the Eclipse version 13.7 treatment planning system. The three-angle arrangement in two different sets was designed as following: 1. posterior and two posterior oblique angle (PPO), 2. posterior and two anterior oblique angle (PAO) . The dose of 6996 cGy, and 5412 cGy in 33 fractions prescribed to the target in high-risk and low-risk areas, respectively. However, 80% of them have metal artifact reduction (MAR) will affect the accuracy of dose delivery.

The similar coverage of the target volumes in high-risk (P=0.0721) and low-risk areas (P=0.333) and also the mean dose of oral cavity (P=0.368) and larynx(P=0.093) were observed in different sets of three-angle beam arrangement. But the PAO provided lower maximum dose in brainstem (P=0.017) and spinal cord (P=0.013). The PRO provided lower mean dose left and right parotid gland (P=0.043 and P=0.045), and lower maximum dose in mandible (P=0.007).

The dose comparison in two sets of three-angle beam arrangement exhibited different advantages and disadvantages in patients with NPC. However, dose uncertainty is often caused by dental artifacts and implants in head and neck cancer. Therefore, to select optimized beam angles for NPC patients treated with MFO-IMPT should be considered to minimize the dose uncertainty produced in beam path.

PTC58-0115

Dose comparison of pencil beam scanning (PBS) carbon-ion and VMAT technique for parotid carcinoma

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Purpose: To study the dosimetric advantages of a comparison between PBS intensity-modulated carbon-ion therapy (IMCT) versus VMAT for parotid gland cancers.

Materials and Methods: Reviewed 8 parotid carcinoma patients treated with IMCT between 2017-2018, prescription dose was 54Gy (relative biological effective dose, RBE) to CTV while SIB tumor bed to 63Gy (RBE) in 18 fraction, each patient IMCT plan use one oblique beam with range shifter, one VMAT plan was generated for dose comparison, which use two partial Arcs for dose conformity. Dosimetric comparisons for each organ at risk were evaluated by using two sample T-test, with $P < 0.05$considered statistically significant.

Results: Both VMAT and IMCT have 90% prescription dose covered at least 95% volume of PTV for target, while 95% prescription dose covered at least 95% volume of the target. IMCT compared to VMAT, significantly reduced the mean dose to OARs: brain stem(15.75 versus 20.2 Gy (RBE), P=0.244) , ipsilateral cochlea (14.19 versus 21.5 Gy (RBE), P=0.508), contralateral cochlea (1.22 versus 6.65 Gy (RBE), P=0.008), oral cavity (6.12 versus 28.76 Gy (RBE), P=0.0001), larynx (6.45 versus 21.56 Gy (RBE), P=0.0001), contralateral parotid gland (0.035 versus 7.6 Gy (RBE) , P=0.002), spinal cord(12.4 versus 19.72 Gy (RBE), P=0.031), Body-PTV (3.84 versus 11.97 Gy (RBE), P=0.000006)

Conclusion: IMCT have superior normal tissue sparing while still maintaining excellent target coverage for parotid gland cancer, and significantly lower Body integrate dose. Clinical outcomes with PBS carbon-ion therapy needs long term follow up.

PTC58-0019

Upgraded analyses for the effect of organ motion on proton prostate treatment using full sets of daily CT images

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Purpose: To quantify the effect of interfractional movements of the prostate, seminal vesicles (SVs) and rectum on prostate proton treatment using full sets of in-room CT images.

Methods: We analyzed 1483 sets of daily CT images acquired throughout the proton therapy treatment for 40 patients with four time's higher statistics than the one of our published results [1]. We evaluated daily movements of pelvic anatomies by simulating image-matching strategies, and estimated means, systematic and random errors of each anatomies. The change of the mean and errors were also studied by referring daily CT-images as a reference to evaluate the optimum period of re-acquiring the CT-images for re-planning.

Results: The data confirmed our previous results and the prostate-rectum matching showed the smaller errors. The mean and systematic errors of the anterior and posterior sides of SVs decreased, when the daily CT-images acquired around 10 days after the first irradiation were used as a reference in comparison to the simulator CT-images, as did the rectum's anterior region. Figure 1 shows the mean and errors of the rectal daily movement over the superior-inferior (SI) position by referring sequential daily CT-images for each image matching method. The positive mean values around SVs region, which means the movement toward the anterior side, decreased gradually as the reference CT number increases.

The re-planning with the reference CT after 10 days might reduce the rectal dose around SV region. The effect of daily movement on proton dose will be presented based on several planning scenarios. [1] Y.Maeda, *et al*. Medical Physics,45(5),1844(2018).

PTC58-0338

Characterizing dose perturbations due to various uncertainties during PBS proton therapy for breast cancers with IMN and nodal involvement

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Purpose: To evaluate dose perturbations during breast PBS proton therapy due to repository motion and changes in breast seroma size.

Methods: To evaluate dose perturbation due to breathing motion, hypothetical breast/nodal target volumes were created on 5 female patients with 4DCTs. The target and OAR contours from the planning CT were propagated onto the 10 individual 4DCT phases and the PBS proton breast plan was recalculated on the 10 phases, to evaluate changes in target coverage and OAR doses due to breathing motion. To evaluate the effect of changes in seroma size, a different cohort of 5 patients were selected: previously treated breast patients who had seromas present at the start of radiotherapy and had additional simulation CTs during radiotherapy. Proton plans were generated on the original planning CT and the dose was recalculated on the repeat CT(s), to evaluate the effect of increase/decrease of seroma size on target volume coverage and OAR doses.

Results: Perturbations in target coverage due to breathing was minimal and variations in dose to OARs was within an acceptable range. The effect of changes in seroma size was more variable and dependent on location of the seroma and magnitude of size increase/decrease. An increase in seroma size could cause clinically significant loss of coverage, whereas a decrease in seroma size caused overshooting of the proton beam into normal tissue/OARs.

Conclusion: Dose perturbation due to breathing is not clinically relevant. However, the presence of seromas may require pre-emptive action, like larger planning margins for the seroma or regular rescanning for dose recalculation/evaluation.

PTC58-0431

Dosimetric validation of spectral CT-based stopping power prediction for proton beams using an anthropomorphic head phantom

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Purpose: To establish and validate a novel method for stopping-power ratio to water (SPR_w) prediction protocol for improved proton beam range prediction.

Methods: Calibration measurements were acquired using phantoms with various tissue-equivalent inserts (Gammex 467) on the Philips IQon Spectral CT system to derive three-dimensional maps of SPR_w based on effective atomic number and electron density relative to water. Validation in a clinical-like setting was performed using a half-head Alderson RANDO phantom attached to a water tank. After conventional planning based on a standard CT (Siemens SOMATOM Confidence RT Pro), optimization was performed with a Monte Carlo treatment planning platform. A target structure (6 cm $\times$ 6 cm $\times$ 6 cm, centered at 5 cm depth) was delineated for spread-out Bragg peak (SOBP) optimization. Dose calculation was performed on both the conventional planning CT and spectral CT. Absolute dosimetry was performed in the experimental beam room using a PinPoint ionization chamber block for range verification.

Results: For the tissue surrogates, SPR_w predicted from spectral CT images was within a mean accuracy of $<$1 % compared to measured SPR_w. Mean deviation in range between the two SOBP calculations using the half-head anthropomorphic phantom was roughly 1.3($\pm$2.6) mm.

Conclusion: Preliminary results for SPR_w prediction with spectral CT data show promise over that of conventional means for proton range estimates for high-precision radiotherapy.

PTC58-0597

Dosimetry comparison of IMRT, VMAT versus proton and carbon ion pencil beam scanning techniques for tongue cancer

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Objective: To evaluate dose difference between photon and particle radiotherapy (carbon and proton) for tongue cancer

Methods: Five head and neck cancer patients suffering tongue cancer were involved. Treatment plans based on intensity modulated proton therapy (IMPT), intensity modulated carbon therapy (IMCT), intensity modulated photon therapy (IMRT) and volumetric modulated arc therapy (VMAT) were designed to give a similar dose distribution to the clinical target volume (CTV). Dose deposited in contralateral parotid (mean dose, V30GyE), spinal cord (D1%) and brainstem (D1%) were evaluated in this study.

Results: The dose coverages of CTV in four modalities were comparable and 95% prescription dose covers at least 95% volume of the CTV. The mean doses of contralateral parotid could be reduced from 27.3GyE (IMRT) and 27.7GyE (VMAT) to 19.4GyE (IMCT) and 20.7GyE (IMPT) in average. V30GyE could be also reduced by 23.3% in the particle plans. The D1% of spinal cord (brain stem) in IMRT and VMAT were 21.7(9.8)GyE and 20.8(10.5)GyE while D1% of spinal cord (brain stem) were 13.6(3.6)GyE and 13.8(2.8)GyE in IMCT and IMPT plans.

Conclusion: IMPT and IMCT has shown a better dose conformity to the target and are capable of reducing the doses in the OARs. However, the dosimetric advantages of ion radiotherapy for tongue cancer still needs clinical verification.

PTC58-0598

Dosimetric advantages of particle radiotherapy for retroperitoneal soft tissue sarcoma: Comparison between proton, carbon ion, photon IMRT and VMAT techniques

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Objective: To evaluate the dosimetric advantages of particle radiotherapy for retroperitoneal soft tissue sarcoma after surgical resection with different radiation modalities

Methods: Seven patients with retroperitoneal soft tissue sarcoma and underwent surgical resections of their affected kidneys were enrolled in this study. Particle plans were made based on intensity modulated proton therapy (IMPT), intensity modulated carbon therapy (IMCT). Two types of photon plans were designed based on intensity modulated photon (IMRT) and volumetric modulated arc therapy (VMAT) separately. Patient's duodenum, contralateral kidney and stomach doses were evaluated.

Results: Four modalities could achieve a similar dose coverage of 95% prescription dose covering PTV. Compared with IMRT and VMAT, IMCT and IMPT could significantly decrease the maximum doses patients' stomach, duodenum and contralateral kidney (shown in Table 1). In addition, 26.8% and 34.8% of the duodenum could be spared from 10GyE in IMCT and IMPT than VMAT plans. The mean doses of patients' contralateral kidneys were 23.3±26.3 GyE, 37.3±54.9 GyE, 333.2±152.1 GyE and 363.6±147.9 GyE in IMCT, IMPT, IMRT and VMAT plans.

Conclusion: Compared with IMRT and VMAT techniques, IMPT and IMCT can decrease the dose to patients' upper gastrointestinal tract effectively. Particle therapy indicates their dosimetric superiority to photon therapy, while dosimetric advantages needs clinical verification.

PTC58-0381

Ion stopping powers and dual energy CT numbers of animal tissues for Monte Carlo dose calculations

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Purpose: For ion beam treatments, most treatment planning systems (TPSs) use a pencil beam algorithm that calculates dose distributions using depth dose data measured in water and an algorithm that converts the x ray computed tomography number of a given material to its linear stopping power relative to water (RLSP). Recently some TPSs have started using Monte Carlo type dose calculations. These calculations typically need the physical density and elemental composition of the tissues to determine penetration and calculate dose.

Methods: Samples of 10 different animal tissues were obtained and packed in regularly-shaped containers. The physical density of each sample was measured. The samples were then scanned one at a time with a dual energy CT scanner. In addition, the samples were placed between the exit of a beamline and a variable length water column to measure single-spot integrated depth dose distributions. Beams of protons accelerated to energies of 116.0, 165.3, and 221.1 MeV and carbon ions accelerated to 216.7, 322.8, and 430 MeV/n were used.

Result: For each tissue a dual-energy CT index was derived.[1] This index may be used for determining the elemental composition classification for each tissue used in the Monte Carlo calculations. RLSPs were derived for each tissue for verification of the correct conversion function.

Conclusions: Data for converting dual energy CT numbers for Monte Carlo dose calculations were obtained as well as data for verifying the correct conversion.[1]Wang, A. S. Hsieh, S. S. Pelc, N. J. (2012) ‘‘A dual energy CT: principles, applications, and future outlook’’

PTC58-0053

Validating a new treatment planning system for accelerator-based BNCT

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Sumitomo has been developing the accelerator-based BNCT system, and clinical trials (Phase II) for recurrent brain tumors and recurrent head and neck cancer have been conducted with our machines toward world-first medical device approval in Japan. We also have been developing the treatment planning system (TPS) in order to improve accuracy and usability of treatment planning in BNCT. BNCT planning essentially requires Monte Carlo calculation for precise neutron transportation. Our TPS employs PHITS as a Monte Carlo dose engine. In this research, we measured neutron fluence and validated dose calculation accuracy of our TPS. The dose components of BNCT can be categorized into the following four factors:

1) $^{10}B(n, \alpha)^{7}Li$ reaction
2) $^{1}H(n, n')^{1}H$ reaction
3) $^{14}N(n, p)^{14}C$ reaction
4) gamma-ray from beam port and secondary gamma by $^{1}H(n, \gamma)^{2}H$

There is no established method of directly measuring the doses from (1) - (3) reactions. Therefore, thermal neutron fluence which is proportional to the neutron doses was measured by activation method with gold and cadmium. Gamma ray dose was measured by TLD.

As a result, the calculation from TPS agreed with the measurements within the range of error. It was confirmed that our TPS has sufficient accuracy for BNCT planning.

PTC58-0715

Evaluation of treatment plans based on the Mevion Hyperscan beam characteristics

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Purpose: To investigate treatment plans generated using the Raystation RS6 based on the Mevion Hyperscan beam characteristics and compare the results with traditional beam-line based proton systems

Method: Clinical plans generated for patient treatments at GUH from March, 2018 to December, 2018 were analyzed for different treatment sites. Plan parameters evaluated include clinical goals specified by the clinicians, volumetric and planar dose distributions. Treatment plans using the same beam configurations were regenerated for an IBA proton system and compared with the Hyperscan plans using the Raystation plan comparison feature. In particular, dose distributions in proximal, distal and lateral regions were evaluated comparatively.

Results and Discussions: All most all treatment plans met the clinical goals set forth by the clinicians-some of them with minor deviations. Unique to the Hyperscan are the constant Bragg peak width and progressively larger spot sizes at lower energies, and an Adaptive Aperture for spot size trimming. Potential impacts of such beam characteristics are mostly reflected in the distal and proximal region, as well as lateral regions. On average, while the AA enables penumbra trimming to meet almost clinical goals on OARs, an excess dose to varying degrees was observed in lateral planes for the Hyperscan plans, although such excess doses were judged to be of no clinical significance by the clinicians. The larger spots size of the Hyperscan were remedied by the use of the effective use of the Adaptive Aperture.

PTC58-0094

Dosimetric impact of residual prostate motion alone based on real-time acoustic tracking information

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Purpose: To investigate dosimetric impact of intra-fraction prostate motion for photon and proton plans.

Methods: Gross directional displacement (4.3mm Inf and 4.8mm Post) was applied to offset the isocenter on a case study (74Gy in 37#, prostate alone) to simulate the impact on VMAT photon (2-Arc) and proton (two lateral-oblique SFUD with 3% range uncertainty) plans using the Eclipse treatment planning system (v13.6). The offset values were inferred from the trends of shifts derived from the real-time intra-fraction prostate motion tracking using a 4D transperineal ultrasound system previously published (n=55, 1744 fractions) [Pang et al.,2018]. Both treatment plans had dosimetric impact simulated based on the applied geometrical offsets and subsequently compared with the pre-offset scenario for CTV (prostate) coverage and doses to the OARs (bladder and rectum).

Results: D95 of the prostate was reduced from 74.4Gy to 73.9Gy (-0.7%) and from 74.3Gy (RBE) to 71.1Gy (RBE) (-4.3%) for the photon and proton plans, respectively with the simulated offset. However, D95 of prostate for the proton plan achieved 74.1Gy (RBE) when plan uncertainties of the offset were incorporated. Mean dose to the bladder decreased by 5.5Gy and 1.6Gy (RBE); mean rectum dose increased by 6Gy in the photon and decreased by 1.1Gy (RBE) proton plans with offset.

Conclusion: 2-Arc VMAT photon plan is less susceptible to the impact of intra-fraction prostate motion compared to 2-field SFUD proton plan. Incorporating intra-fraction motion uncertainties within the plan uncertainty parameters should be considered despite daily online image guidance and setup corrections in proton treatment.

PTC58-0387

In vitro measurement and modeling of the oxygen enhancement ratio for carbon ion therapy

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Tumor hypoxia is one of the limiting factors for tumor control in ion beam therapy. The reduced radiosensitivity of oxygen-deprived cells has been correlated with treatment failure. Hence, accounting for the oxygen effect in treatment planning is of great importance. However, *in vitro* data taken under hypoxic conditions, which serve as the basis for radiobiological models, are scarce. Additional biological measurements are, therefore, extremely needed. In this work, cell survival measurements on human salivary gland (HSG) tumor cells subjected to oxygen tensions of 159.6, 7.6, 3.8, 0.8 and 0 mmHg are presented. In the experiments, HSG cell samples were irradiated with a 290-MeV/n carbon beam at dose-averaged LET values of 17, 27, 57 and 71 keV/μm. The data were pooled together with published HSG data and used on two different modeling approaches. The first scheme models the linear-quadratic (LQ) model parameters as a function of the oxygen concentration and LET. This approach allows the convenient computation of the oxygen enhancement ratio at any survival level. Alternatively, the modified stochastic microdosimetric kinetic (SMK) model was considered. The SMK model accounts for the stochastic nature of energy deposition both in the microscopic subnuclear structure domain and cell nucleus to characterize the survival fraction of cells from charged-particle beams. The dependence of SMK model parameters on the oxygen concentration were derived based on the HSG cell dataset. This adaptation of the LQ and SMK models to hypoxia provides an opportunity for a refined biological optimization in treatment planning for carbon ion therapy.

PTC58-0319

Towards the automation of PBS proton treatment planning

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Purpose: To develop an automatic planning process for intra-cranial PBS proton treatments.

Materials and Methods: Phase one (Fig. 1) consists in the automatic selection of all clinically feasible gantry and couch angles setup (GCAS), based on the target localization. This is achieved either via a class solution (CS) or via a computation of heterogeneity index (HI) of the possible beam paths. CS allows the user to select the anatomical region and therefore a predefined setup suggested by experts. Selecting AHI, all available GCAS, based on the heterogeneity index extracted for each beam path angles, are listed (Fig. 2). The user may then select from 2 up to a maximum of 4 fields, with a minimum separation of 30°, as well as the use of range shifter for each field. Target homogeneous dose coverage is then obtained by either PBS single field or multiple field optimization. In the undergoing phase two, genetic algorithm (GA) gets as input the optimal GCAS from the CS and AHI option and, in addition to target coverage, includes OAR sparing, using as the chromosomes of the algorithm the max equivalent uniform dose function for brainstem, spinal cord, optical chiasm and nerves.

Results and Future Work: Phase one lead to a fluid and intuitive workflow to achieve the best GCAS, based on the CS or AHI option, and a clinical acceptable homogeneous target dose coverage. The upcoming results of phase two will allow to validate the clinical use of GA proton auto-planning for intra-cranial tumors.

PTC58-0372

Dosimetric impact of volumetric modulated arc therapy for synchronous bilateral breast cancer: Comparison with intensity modulated radiation therapy

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Aim: To study the dosimetric impact of Volumetric Modulated Arc Therapy (VMAT) for Synchronous Bilateral Breast Cancer (SBBC), patients treated with breast conserving surgery and definitive irradiation were compared with Intensity Modulated Radiation Therapy (IMRT).

Methods and Material: Ten patients of SBCC [Stage I & II (N_0M_0)] were used for this study retrospectively. IMRT and VMAT plans were done in CMS, Monaco, (V.3.30.1) TPS with Elekta Synergy with MLCi2.Target volumes {Separate PTVs (RT &LT)} and OARs were done using RTOG guidelines.50Gy in 25# was prescribed to PTV. The parameters evaluated included the doses to organs at risk, dose homogeneity and Conformity Index (CI), and monitor units required for delivery of a 2-Gy fraction.

Results and Discussion: Acceptable plan quality was achieved for both the plans Significant differences were observed in V5, V10, V20, and V30 for both the lungs. Heart mean dose was reduced 36 % by VMAT than IMRT. VMAT Offered lesser MU than IMRT but no significant differences. VMAT reduced treatment time by 51% than IMRT (9.75$\pm$ 2.4 Vs 4.93 $\pm$ 0.63) mins . VMAT showed slightly lesser mean dose for unspecified tissue than IMRT. Single Isocenter plan reduced the plan complexity. VMAT achieved slightly better target coverage. IMRT showed better HI than VMAT. Conformity Index (CI) was improved with VMAT Compared with IMRT.

Conclusion: VMAT performed better than IMRT for the reduction dose to lungs and Heart. VMAT achieved shorter treatment time than IMRT for Synchronous Bilateral Breast Cancer without compromising the plan quality.

PTC58-0708

Proton therapy and deep inspiration breath hold for optimal radiotherapy for patients with thymoma

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Thymoma is a rare malignancy of the thymus, occurring in 0.13 per 100,000 persons/year (SEER 2006). Substantial knowledge exists from lymphoma patients that radiation dose to the organs at risk (OARs) in the mediastinum results in increased morbidity and mortality. A few studies have reported promising results for proton therapy for thymoma, but data is limited. Furthermore, the benefit of the combination of deep inspiration breath hold (DIBH) and proton therapy for thymoma has not been studied, which was our aim in this study. We created plans for 8 thymoma patients in free breathing (FB) and in DIBH for volumetric modulated arc therapy (VMAT) and intensity-modulated proton therapy (IMPT) for a prescription dose of 50 Gy (RBE). For VMAT plans CTV-to-PTV margins were 1 cm for DIBH and 1.5 cm superior-inferior and otherwise 1 cm for FB. IMPT plans were created using robust optimization and evaluation (4.5% CT calibration and 5 mm positioning uncertainty for FB and DIBH, $D_{98\%}>90\%$ for all scenarios and $D_{98\%}>95\%$ for 10/12 scenarios for the CTV). Mean doses to the heart and lungs were compared. We found that, on average, IMPT in DIBH yielded the lowest doses to the heart and lungs. Details of OAR doses are shown in Table 1, and IMPT generally reduced the volume of lungs exposed to a lower dose (Figure 1, patient 3). In conclusion, both DIBH and IMPT reduced the dose to the heart and lungs for the thymoma patients in this study relative to VMAT in FB.

PTC58-0453

Feasibility and dosimetric improvement of radiosurgical pulmonary vein isolation for atrial fibrillation using intensity-modulated proton therapy (IMPT)

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Purpose and Objectives: Stereotactic radioablation targeting veno-atrial junction (LA-PVJ) has been demonstrated safe and effective in experimental models. IMPT has potential to spare of surrounding tissue due to its sharp distal dose fall-off. In this study, we simulated the treatment planning, then evaluated the feasibility and dosimetry between IMPT and intensity-modulated radiation therapy (IMRT).

Materials and Methods: Five thoracic 4D-CT simulation scans were taken every 10% of the respiratory cycle with and without contrast-enhanced. The targets at the LA-PVJ were contoured as wide-area circumferential ablation line. A total dose of 25 GyE in a single-fraction was prescribed to ITV using 3-4 beams in IMPT (PBT) and 10-14 coplanar beams in simulating spot-scanning proton arc therapy (PAT). IMRT used 9 beams and received 25Gy to PTV. Both proton therapy plans were generated using robust optimization to achieve optimal coverage with 99% ITV. Statistical analysis was evaluated via one-way Repeated-Measures ANOVA.

Results: The median volume of ITV was 6.33±4.29cc. No differences were found in D_{mean}, D_{95} and HI of ITV between IMRT and IMPT. Compared with IMRT, IMPT resulted in significantly lower Lung $V_{2.5}$, D_{mean} of heart and LCX, but not $D_{0.03cc}$ of cord and bronchus. Results were summarized in table 1.

Picture-"Table. DVH parameters (Mean±SD) of the ITV and OARs."

Conclusion: Treatment planning of IMPT targeting LA-PVJ for patients with atrial fibrillation is feasible and showed comparable high dose conformity and homogeneity, while excellent sparing of heart and cardiac substructures than IMRT. However, the dosage of esophagus and bronchus adjacent to ITV requires more attention and further research.

PTC58-0186

Implementation of automated knowledge-based tool for treatment of skull-base chordomas with PBS proton therapy

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Due to their close proximity to critical OARs, skull base chordomas (SBC) are challenging tumors, for which proton therapy has long been established as the standard of care. RapidPlan™ (RP) is a knowledge-based tool capable of predicting target volume and organ-at-risk (OAR) dose-volume histograms (DVH) based on models built from anatomical information, beam geometries and dose distributions. In this study, we evaluate the performance of RP for modeling and planning pencil beam scanned proton SBC treatments. Twenty-five cases, all calculated using our in-house planning system, were randomly selected and used to train two independent RP models, according to the cone-down technique used at our center (plan 1 up to 54GY(RBE) and plan 2 from 54-74Gy(RBE)). The models were further enhanced using additional, manually-defined constraints to the brainstem, optic structures and spinal cord. The model was tested using eight additional cases and results compared to the original plans. For the PTV54/CTV54, coverage (V95%) was identical, whereas to the PTV74/CTV74, V95% increased on average by 7.3% and 8.4% respectively using RP. All critical OARs met constraints and were on average reduced using RP (table 1, figure 1). In conclusion, even with models derived from data from a different TPS, RP is a promising solution for planning SBC cases. It could be used as tool for quality benchmarking of manual plans and to provide a quick indicative plan for referring centers. An optimization of the second plan based on the outcome of the first one could further enhance the outcomes of RP.

PTC58-0224

An automated treatment planning method based on overlap-volume-histogram metric

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The aim of this study was to investigate that whether OVH metrics can serve as metric for automated treatment planning by evaluating the plan quality for cervical patient. Twenty Cervical patients were enrolled for modeling where authors quantify the geometrical relationship between OARs (bladder, rectum, cord, bowel and femoral heads) and the PTV separately using an OVH metric which determines the fractional volume of the OARs that is within a specified distance of the PTV. For an OVH distance the authors selected L(x) which means the PTV expansion distance at which X% of the OARs overlaps, where the value of x is depended on organ clinical goals. The authors calculated all OARs dose Dx correspondingly from the dose volume histogram (DVH). Regression model was created by analyzing the correlation between the L_x and D_x for all OARs. For new patient, we extracted OVH getting Lx and utilized the regression model to generate Dx, then set that as optimization objective engine to start auto-planning. Results: Quadratic polynomial correction was found between Lx and Dx for femoral heads and cord (R2 =0.65, 0.77, respectively), where x were 20,30,50,80 for femoral heads while were 0,5,10,20 for cord. In addition, linear regression showed an inverse linear correlation or bladder, rectum and bowel (R2 =0.33,0.56,0.85, respectively), where x were 50,70,80,90 for bladder and rectum, while were 10,20,30,50.80 for bowel. The relationship between Lx and Dx presented that OVH metric was an effective indicator for dose prediction. Application of OVH metrics to automated planning produced acceptable treatment plans.

PTC58-0654

Biologically relevant predictions for proton beam therapy from in silico modelling and the relevance to treatment planning

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Clinically, the Relative Biological Effectiveness (RBE) of protons compared to photons is 1.1. However, large variance exists in the studies informing this value. It has been shown that RBE is variable and depending on factors including dose and Linear Energy Transfer (LET).

Previous work has presented the results of an *in-silico* model which investigates some of the parameters that determine RBE. Detailed models of the DNA and the cell are constructed in Geant4-DNA where the DNA energy depositions, resulting from track-structure, are recorded. Mechanisms of direct and indirect DNA damage are incorporated by simulation and comparison to experimental data. Resulting DNA damage data is then passed to our model of DNA repair where predictions on kinetics and fidelity of DNA repair are made.

The model predicts an increase in complex damages and misrepair events in Double Strand Break (DSBs) repair with LET and that biological outcome is dominated by residual DSBs across the LET range. A series of correlations are established that relate dose and LET to the biological outcomes predicted by the detailed models.

In this work, we have used GATE to simulate a proton treatment plan of an ependymoma case. Here, we score dose and LET in each voxel and, using the correlations, we convert the scored parameters into biological predictions, the yields of residual and misrepaired DSBs. This will provide valuable information to the clinician, allowing for the identification of regions of heightened biological effect and is a step towards biologically optimised radiotherapy.

PTC58-0421

Robust intensity-modulated proton therapy with dose-escalated simultaneous integrated boost reduces the low-dose to surrounding tissues in pancreatic cancer patients

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Purpose: This *in-silico* study on simultaneous integrated boost dose-escalation in non-metastatic pancreatic cancer patients dosimetrically compared robust multi-field optimized intensity-modulated proton therapy (IMPT) with volumetric modulated arc therapy (VMAT).

Material and Methods: For five patients, both treatment plans were optimized on free-breathing CTs using RayStation. For VMAT, at least 95% of the prescribed doses of 66Gy and 51Gy to the boost (GTV) and PTV (CTV+5mm), respectively, were to cover 95% of the targets. For IMPT, robust optimization with a setup uncertainty of 5mm and a density uncertainty of 3.5% was applied to the GTV and CTV, with the aforementioned dose levels (RBE) again covering 95% of the targets. The OAR dose constraints adhered to local guidelines and QUANTEC.

Results: All treatment plans reached the prescribed doses to the targets. Doses to the bowel, stomach and/or liver exceeded at least one constraint in all treatment plans, since those OARs were next to or within the targets. While VMAT reduced the median V_{50Gy} of the stomach, doses to the remaining gastrointestinal organs, e.g. liver and kidneys, were lower for IMPT (Fig. 1). Overall, IMPT deposited less low dose outside the CTV (Fig. 2, median integral V_{20Gy}: 1483.4ccm vs. 756.2ccm).

Conclusion: Disregarding inter- and intra-fractional organ motion, dose escalation with IMPT and VMAT is possible. IMPT reduced the dose to surrounding normal tissues, except for OARs overlapping with the target volume, in which the dose was higher due to the robust optimization approach. Additional patients will be included in this study.

PTC58-0189

Evaluating the quality of radiotherapy treatment plans under uncertainty

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To support the radiotherapy planning process, we seek plans that would benefit from re-optimisation by proposing a method to evaluate the quality of the treatment plans.

Data from prostate cancer patients treated with intensity modulated radiation therapy at Rosemere Cancer Center, Royal Preston Hospital were used. The clinical protocol was translated into a set of measurable variables and statistical techniques were used to select the most relevant variables. We used a management science tool, Data Envelopment Analysis (DEA), to assess the performance of radiotherapy treatment plans relative to other, previous plans. We then evaluated how well the plans performed in terms of achieving the conflicting goals of radiotherapy; that is, to protect the organs at risk while delivering the prescribed dose to the tumor.

Many elements of the treatment process from the delivered dose to treatment machine alignment are inherently uncertain. To account for this uncertainty in the data, we used simulation techniques and robust optimisation. After identifying plans that we believed had the potential to be improved further the plans were returned to clinicians at Rosemere.

Here we discuss the improvements that were seen in the plans and the potential difference this could make to planning more complex cases in the future.

PTC58-0269

Synchronous bilateral breast cancer irradiation: Dosimetric comparison using intensity-modulated radiation therapy, volumetric modulated arc therapy, and intensitiy modulated proton therapy

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Background: Synchronous malignancy in both breasts is a rare incidence. The present study aims at dosimetric comparison of intensity-modulated radiation therapy(IMRT),volumetric modulated arc therapy(VMAT) and intensity modulated proton therapy(IMPT) for patients with synchronous bilateral breast cancer(SBBC).

Methods: For 6 patients with synchronous bilateral breast cancer, three plans were designed: IMRT (12-14 fields with double isocenters), VMAT (8 partial arcs with double isocenters) and IMPT(2 fields with a single isocenter). Plans were designed to achieve 95% coverage of target to a dose of 50 Gy or Gy (RBE) while maximally sparing organs-at-risk. The plans were evaluated based on a dose-volume histogram analysis.

Results: For PTV, IMPT plans showed the best max dose (D2%) and homogeneity. VMAT plans showed the best conformity. Compared to IMRT and VMAT plans, IMPT plans significantly reduced V5,V10 and mean dose to lungs. VMAT plans showed the highest values on V5,V10 of lungs. IMPT plans significantly reduced V5,V10,V20,V30,V40 and mean dose to heart. Compared to IMRT and VMAT plans, IMPT plans significantly reduced V5,V10,V20,V30 and mean dose to left anterior descending and left ventricle. VMAT plans significantly reduced the max dose on left anterior descending.

Conclusions: IMPT plans improved homogeneity to the target and reduced doses to the lungs and heart.

PTC58-0254

Quantitative evaluation method for metal artifact in virtual monochromatic CT image

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Metal artifacts in CT images are a serious problem when predicting an accurate range of proton in treatment planning of proton therapy. Metal artifact reduction techniques are being studied and should be evaluated quantitatively. However, existing evaluation methods strongly depend on noise. The objects of this study are to construct a new evaluation method for metal artifact which is independent of noise and to optimize a virtual monochromatic CT image.

We focused on macroscopic distortion around metal. In the method, we assumed the uniform substance around the metal and considered 24 regions of interest (ROI) around the metal (Fig. 1a). Average pixel values in each ROI represent macroscopic angular distribution (MAD) of metal artifact, which is independent of noise. The standard deviation of MAD (SDMAD) was regarded as the intensity of metal artifact. The standard deviation of surrounding ROI (SDSROI) was also calculated for comparison (Fig. 1b). CT images of a GAMMEX phantom with an additional titanium insert were acquired using Optima 580w (GE) with various energies. Virtual monochromatic CT images were calculated as the linear extrapolation of 80 and 140-kV CT images. Virtual monochromatic CT images with intentional noise were also evaluated.

SDMAD and SDSROI agreed with a visual evaluation in acquired CT images and we optimized virtual monochromatic CT images (Fig. 2). SDMAD was not changed if noise is intendedly added. SDMAD is utilized specifically for metal artifact evaluation.

We established a method to evaluate metal artifact without influence of noise.

PTC58-0402

Temporal lobe sparing radiotherapy for cognitive preservation in pediatric suprasellar brain tumor patients

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Purpose: Reduced radiation exposure to the temporal lobes could be beneficial to preserve cognitive functions following radiotherapy of pediatric brain tumors. We investigated doses to brain substructures associated with cognition (BSCs) in temporal lobe sparing photon vs. proton therapy of pediatric midline brain tumors, and modeled the risk of subsequent potential memory impairments.

Material and Methods: Data from ten anonymized craniopharyngioma patients were used. Temporal lobe sparing volumetric modulated arc therapy (VMAT) and pencil beam scanning proton therapy (PBS) plans were optimized to maintain consistent target metrics as in the clinically delivered double scattering proton therapy (DSPT) plans. Thirty BSCs were delineated, including temporal lobe substructures (i.e. amygdala, hippocampus, entorhinal cortex) and BSCs outside of this region. The dose/volume fractions to each BSCs were analyzed, and memory scores were estimated to compare the three modalities. Wilcoxon signed-rank tests were used to compare the modalities.

Results: The irradiated volumes of temporal lobe and their substructures were consistently reduced with PBS, e.g. from 100% (VMAT) and 41% (DSPT) to 5% for the left hippocampus V10Gy ($p<0.002$), and from 41% (VMAT) and 43% (DSPT) to 24% for the left amygdala V40Gy ($p<0.02$) (Fig. 1). Some of the ventricular substructures were better spared with VMAT compared to both proton modalities. Overall, the reduced temporal lobe doses translated into lower estimated risks of memory impairment with PBS (Fig. 2).

Conclusion: The irradiated volumes of temporal lobe BSCs were consistently the lowest with PBS, with better predicted memory outcomes for the patients.

PTC58-0696

A WebGL based visual proton delivery simulator

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Purpose: Planning proton therapy is complicated because setup, organ motion, and range uncertainties affect dose delivery, dependent on beam directions and optimization. For understanding robustness of plans, a fast delivery simulator would be beneficial, and here we develop one.

Methods: Full dose calculation is impractical, but using a core assumption that individual beams can move and deform relative to each other with range variation, calculation of treatment scenarios that correctly render delivery variation at depth is possible. The system runs in a web page on the GPU, using WebGL. WebGL code consists of a C-like program that is integrated in the web page code and evaluated massively parallel for every pixel on the screen. Input data (CT and beam doses), are provided as a few large texture images (e.g. Fig. 1, cutout), calculated on the server. Sliders allow setting the delivery and error parameters.

Results: The core of the shader program is only 50 lines. WebGL runs about 100 times faster than Javascript. Figure 2 shows a mock proton plan in the resulting web page, where dose inhomogeneity due to range uncertainties per fraction is simulated - fast. Even on a low-end graphic card a 20-fraction treatment is simulated at 60 fps, providing immediate feedback on a change of parameters.

Conclusions: We demonstrated that it is possible to provide a realistic simulation of proton delivery in a web page that is suitable as training tool. Evaluation of the simulation accuracy for clinical robustness evaluation remains to be done.

PTC58-0664

Calculation of IMPT plan robustness

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Intensity modulated proton therapy using pencil beam scanning technique is most promising approach of proton treatment delivery. It allows creation of very complex dose distribution with steep gradients areas. With all its advantages risk of misplacement of dose inside patients is of interest. Robustness of treatment plan is its property that scores mentioned risk. To be able to score individual plan robustness we would like to present deterministic method of calculation of plan robustness index which may have influence on clinical decision about accepting the plan for treatment. This work is supported by INAFYM project CZ.02.1.01/0.0/0.0/16_019/0000766

PTC58-0405

Feasibility assessment of proton treatment for ventricular tachycardia disease: A treatment plans comparison study

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Purpose: To assess the feasibility of single fraction ablative irradiation for ventricular tachycardia (VT) disease by different radiotherapy modalities and techniques.

Materials and Methods: Five common recurrent VT regions: apical anterior, apical inferior, basal septal, inferior basal, lateral basal and nearby organs at risk were contoured by cardiology physician and radiologist familiar with cardiology images. The target dose coverage and dose in organ at risk (OAR) by using photon VMAT with three partial arc, two field proton wobbling (PW) and proton pencil beam (PPB) scanning treatment technique were evaluated respectively.

Results: The average of mean radiation dose to heart, left ventricle, contra-lateral lung and ipsilateral lung in five regions are 416.2cGy, 855.9cGy, 51.5cGy, 81.04cGy in VMAT, and 279.7cGy, 613.4cGy, 0.1cGy, 5.36cGy in PW and 301.5cGy, 446.9cGy, 0.1cGy, 40.8cGy in PPB. The areas of low dose ($V_{20\%}$) in heart and contra-lateral lung are 481.1 cc, 227.8 cc, 218.5 cc and 134.4 cc, 7.2 cc, 7.9 cc in VMAT, PW, and PPB respectively. The conformal indexes among three techniques are similar 1.2, 1.5, and 1.3.

Conclusion: Using proton or photon to treat VT disease might be feasible in planning study, but there have some issues in term of patient localization, target margin defined for respiratory and heartbeat motion, dose measurement and verification for small field irradiation should be realized carefully before clinical application.

PTC58-0482

E-Poster Viewing - June 13 - 15
Background dose compared to robust optimization to create gradient matches in proton craniospinal irradiation (CSI)

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Purpose: A dose gradient between cranial and spinal fields can be generated with robust optimization combining uniform dose constraints and independent ISO shifts between fields (RO method). However, when more than one cranial field is used, it is difficult to control the dose contributions from each field in the junction region, which may decrease robustness. An alternative method uses dose fall off function at the junction region to create desired dose contributions (gradient) from the cranial fields. This dose contribution is then used as a background dose for the spinal field (BD method). We compared the dosimetric parameters and robustness of these two planning methods.

Methods: Seven patients were planned with both methods. Prescription was 36Gy in 20 fractions. All plans were normalized to V100 = 98%. Max dose (Dmax), D95, and the robustness of their percentage changes at their worst-case scenario (Max_Delta_Dmax and Max_Delta_D95), as well as their average over all scenarios (Average_Delta_Dmax) were tested. Fourteen scenarios were tested: ±3mm ISO shift in AP, LR, and SI directions, ±3°rotation in roll, pitch, and yaw directions, and ±3.5% range uncertainties.

Results: The max dose and D95 for all nominal plans were 105.7%±0.9% vs 106.8±1.3%, and 100.9%±0.3% vs 100.6%±0.4%, respectively, for RO plans vs BD plans. For all scenarios, Max_Delta_Dmax, Max_Delta_D95, and Average_Delta_Dmax are significantly higher with the RO plans than those with BD plans, 24.3%±10.0% vs 4.4%±2.8% (p=0.003), -7.8%±5.0% vs -0.4%±0.3% (p=0.002), and 10.2%±1.8% vs 7.5%±0.9% (p=0.004), respectively.

Conclusions: CSI plans generated with the BD method were significantly more robust than those created with the RO method.

Physics: Treatment Planning Poster Discussion Sessions

PTC58-0017

Robust optimization for intensity-modulated proton therapy with soft spot sensitivity regularization

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We present a novel IMPT robust optimization method by integrating dose fidelity term with spot sensitivity regularization. The latter robustness term penalizes the inner product of scanning-spot sensitivity and intensity. The sensitivity of a scanning-spot to perturbations is defined as the dose variation from range and positioning errors, and evaluated by the spatial gradient of dose distribution. The sensitivity is then determined by the total absolute value of the directional gradients of all affected voxels. This sensitivity-regularized method (SenR) was tested on three skull-base-tumor (SBT) patients and three head-and-neck (H&N) patients, and implemented on both CTV and PTV. They were compared with conventional PTV-based method (Conv) and CTV-based voxel-wise worst-case scenario approach (WC). Without uncertainties, the SenR-CTV approach achieved better OAR sparing compared with the WC method, reducing [Dmean, Dmax] by [3.63, 3.68] GyRBE, and the OAR sparing of SenR-PTV was comparable with WC (Figure 1). Figure 2 shows the DVH bands of the H&N#2 patient with errors. With range uncertainties, similar or more compacted CTV bands were observed in the SenR-PTV plans compared with the WC plans. The SenR-CTV plans also resulted in narrow CTV bands, but there was a slightly larger underdosage region in the CTV. The robustness against setup uncertainties was similarly improved by SenR-PTV and SenR-CTV. The runtime of SenR is eight times shorter than that of the WC method. In conclusion, we developed a novel computationally efficient IMPT robust optimization method, which showed remarkable flexibility between dosimetry and robustness.

PTC58-0318

Spot-scanning proton arc therapy (SPArc) versus intensity modulated proton therapy (IMPT) for parotid sparing in unilateral tonsil cancer

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Introduction: Lateralized tonsil cancer is a common head and neck cancer, often treated with irradiation to only one side of the neck. IMPT helps spare midline organs such as brainstem and larynx from exit dose, but it is difficult to spare the ipsilateral parotid gland from entrance dose. This is the first known study of unilateral neck irradiation to evaluate potential dosimetric improvements beyond IMPT by using SPArc.

Materials and Methods: Five patients undergoing high dose (66-70 CGE) IMPT using single-field uniform dose (SFUD) optimization for tonsil cancer and the unilateral neck were re-planned using SPArc in RayStation ver. 6.2. The same worst-case-scenario robust optimization parameters were used (3.5% range and 3 mm setup uncertainties, totaling 21 scenarios). Clinical IMPT plans with 2 to 3 fields were compared to SPArc plans utilizing one partial arc with 2.5-degree arc sampling frequency.

Results: Mean dose levels (in CGE) for organs at risk were as follows with IMPT versus SPArc, respectively: Parotid Gland 54.8 vs. 21.8, Pharyngeal Constrictors 43.4 vs. 33.6, Larynx 23.8 vs. 14, Ipsilateral Cochlea 11.6 vs. 2.4, and Esophagus 19.5 vs. 12. Similarly, the average Brainstem maximum was reduced from 25.8 to 15.1 CGE with SPArc. Differences were statistically significant ($p<0.05$) for brainstem, larynx, pharyngeal constrictors, and parotid.

Conclusions: For tonsil cancers requiring unilateral high-dose irradiation, SPArc significantly reduced dose levels to larynx, brainstem and pharyngeal constrictors by nearly 10 Gray beyond clinical IMPT plans. SPArc provided new and clinically meaningful parotid sparing (mean parotid dose 21.8 CGE), thus reducing risks of symptomatic xerostomia.

PTC58-0062

Effect of breathing motion on robustness of proton therapy plans for left-sided breast cancer patients with indication for locoregional irradiation

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Purpose: To investigate dosimetric impact of breathing motion on robustly optimised proton therapy treatment plans for left-sided breast cancer patients with an indication for locoregional irradiation.

Materials and Methods: Clinical Target Volumes (CTVs) (left-sided breast, level 1 to 4 axillary lymph node (LN) regions, interpectoral and internal mammary LN regions) and organs at risk (heart, lungs and right breast) were delineated on 4D-CTs of five female thoracic patients. After treatment planning to a prescribed dose of 40.05 Gy(RBE) in 15 fractions was made on the time-averaged CT, the dose was calculated on all ten phases of the breathing cycle and the robustness to setup and range errors (5mm/3%) was evaluated for those ten phases. Correlations were evaluated between the phases of the breathing cycle and the D98% of the CTV and the Dmean of the heart.

Results: Four out of fifteen of the correlation coefficients turned out to be significant: 0.12 for D98% of the CTVbreast of 1 patient and 0.20, 0.29 and 0.13 for Dmean of the heart of three other patients. At the most extreme values of the 28 robustness scenarios, the clinical goals are met for all patients but one. For this patient, the maximum values of the D2% for the CTVelective exceeded the prescribed dose by 7.7% for all phases of the breathing cycle.

Conclusion: The effect of breathing motion on the robustness of proton therapy treatment plans for this patient group is minor and not of clinical significance. Therefore, deep-inspiration breath hold is not required.

PTC58-0095

Monte Carlo-based multi-field optimization in proton therapy: A new hybrid approach

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Purpose: We present the clinical implementation of a robust multi-field optimization (MFO) technique for pencil beam scanning proton therapy treatments, which is compatible with the application of Monte Carlo (MC) algorithm, including the analysis of its robustness to both physical and biological uncertainties.

Methods: Nine patients (3 brain, 5 head-and-neck, 1 spine) underwent proton treatment generated by a hybrid (hMFO) approach, based on planning dose coverage on a PTV compensating for setup errors, whereas range calibration uncertainties are incorporated in PTV robust optimization process as CT calibration uncertainties. A commercial MC dose calculation engine was adopted. hMFO was compared with single-field optimization (SFO), both by robustness analysis on CTV and organs at risk (OARs) and by assessing in the nominal plans the potential impact of variable relative biological effectiveness (RBE).

Results: Nominal hMFO plans were superior compared to SFO in terms of target coverage ($p=0.004$), without difference for OARs sparing ($p=0.280$). The improvement in target coverage obtained with hMFO (Figure 1) is preserved in worst-case scenarios ($p=0.004$). On OARs, physical (i.e. worst-case scenario) and biological uncertainties (i.e. variable RBE) resulted into significant ($p<0.01$) dose increase for both hMFO and SFO (by 3-7 Gy), but without significant difference between these two techniques (Figure 2).

Conclusions: hMFO allows improving plan quality compared to SFO, without affecting robustness to setup, range and RBE uncertainties. Our data also indicate that uncertainties due to variable RBE, even though generally neglected in clinical practice, might be comparable with those resulting from physical uncertainties.

PTC58-0266

A filtering approach for PET and PG predictions in a proton treatment planning system

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Positron emission tomography (PET) and prompt gamma (PG) detection are promising proton therapy monitoring modalities. Fast calculation of the expected distributions is desirable for comparison to measurements and to develop/train algorithms for automatic treatment error detection. An approach following the formalism of [1] was developed for PET and PG monitoring, and implemented in a research version of RayStation treatment planning system. The implementation accounts for different acquisition time windows and washout effects for PET, and energy selection windows for PG. It can be applied to any tissue, thus being applicable to arbitrary clinical cases. The method estimates positron emitters (PE) and PG at production level and can be coupled with scanners/cameras response models and/or rely on well-established methods to transport energetic (MeV) photons. Validation was done against PET monitoring data and Monte Carlo (MC) simulations for four patients treated with scanned proton beams. Longitudinal shifts between the analytically and MC calculated profiles were within -1.1 and 1.7 mm, with average standard deviation of 0.8 mm and 0.9 mm, for PE and PG shifts, respectively. Normalised mean absolute errors were within 1.2 and 6.2%. Γ-index (1%/1 mm) passing rates were higher than 95% for all cases, except one case with highly complex irradiation scenario. PET case assessment was more robust due to a MC track-length estimator scorer based on experimental cross sections. Calculation times ranged from a few seconds to minutes for an entire patient case, thus proving suitable for clinical use. [1] Parodi and Bortfeld, Phys. Med. Biol., 2006.

PTC58-0350

Dosimetric comparison between carbon-based stereotactic body radiotherapy (SBRT) and photon-based SBRT for early stage, centrally located, non-small cell lung cancer

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Purpose: This study was to investigate the dosimetric differences between carbon ion-based stereotactic body radiotherapy (cSBRT) and photon-based SBRT (xSBRT).

Methods and Materials: Six patients with centrally located early stage non-small cell lung cancer (NSCLC) were planned using 3-dimensional conformal radiotherapy (3DCRT) or ARC technique for xSBRT and pencil beam scanning technique for cSBRT. The prescriptions were 60Gy/5 fractions for xSBRT and 60Gy(E)/5 fractions for cSBRT, respectively. Dosimetric parameters were compared using Wilcoxon signed-rank test. Robust evaluation against setup errors and range uncertainties were conducted for single field uniform dose (SFUD) or robust intensity modulated carbon ion therapy ($IMCT_{robust}$) of cSBRT in one case.

Results: All plans satisfied the target coverage. Conformity Indexes 95% and 50% of cSBRT and ARC-xSBRT were lower than 3DCRT-xSBRT significantly ($p<0.05$). Mean lung dose, mean heart dose, the maximal doses to esophagus and spinal cord were significantly lower in cSBRT compared to 3DCRT-xSBRT and ARC-xSBRT ($p<0.05$). For robust evaluation, the mean dose of target volumes and D95s remained 99% in $IMCT_{robust}$ compared to 96% in SFUD for all tested scenarios. There were no obvious dose changes in organs at risk for both $IMCT_{robust}$ and SFUD plans.

Conclusion: Carbon ion radiotherapy resulted in better sparing of lung, heart, esophagus, great vessels and spinal cord with better target conformity for centrally located early stage NSCLC. $IMCT_{robust}$ was better than SFUD in robustness evaluation in terms of target coverage, while both can keep more than 95% target coverage in tested scenarios.

PTC58-0422

A novel design of proton computed tomography detected by multiple-layer ionization chamber with strip chambers

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Uncertainty in proton range can be eliminated by proton computed tomography (CT). A novel design of proton CT using a multiple-layer ionization chamber (MLIC) with two strip ionization chambers on the surface is proposed to simplify the imaging acquisition and reconstruction.

The strip chambers measured locations and lateral profiles of incident proton beamlets after exiting the imaging object, while the integral of depth dose measured in the MLIC was translated into the residual energy of the beamlet. Simulation was performed at 5 levels of imaging dose to demonstrate the feasibility and performance expectation of our design. Proton stopping power ratio (SPR) was reconstructed through inverse radon transform on sinograms generated with proton beamlets scanning through an imaging phantom from a half-circle gantry rotation.

The reconstructed proton SPR with 5 levels of proton histories per beamlet was illustrated in Figure 1. The maximum deviation in proton SPR from the ground truths was reported slightly larger than the 1% tolerance bar only in one of the 13 inserts when the number of protons per beamlet dropped below 10^3 (Figure 2). Imaging dose was determined to be 0.54 cGy if 5×10^2 protons per beamlet were used for imaging. Imaging quality was acceptable for planning purpose and consistent through all levels of imaging dose. Spatial resolution was measured at 5 line pairs per cm in all simulations varying in imaging dose. Our design is potentially a great tool for dose calculation and plan adaption in proton therapy.

PTC58-0447

Application of 3D printed compensators for pediatric patients in treatment planning of shallow situated head and neck tumors

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Background: Cyclotron PT facilities deliver lowest energy of proton beam between 60 and 100 MeV. Treatment of superficial lesions requires range shifter (RS), increasing spot size, widening lateral penumbra and lowering plan conformity, resulting in decrease of target coverage if sparing organs at risk (OAR). We investigated 3D-printed compensators for pediatric patients to improve dose distribution in treatment planning of shallow situated H&N tumors.

Materials and Methods: Cyclotron Center Bronowice (CCB IFJ PAN, Kraków, Poland) is equipped with IBA Proteus-235 system with RS placed at nozzle exit. Treatment plans for five children with shallow situated H&N cancer were optimized with RS and with compensators printed using Fused-Fiber-Filament (FFF) technology with polylactide (PLA) material. Compensators were examined for homogeneity and range uncertainties. Treatment plans were compared for coverage, conformity and OAR sparing. Influence of intra-fractional patient positioning errors on plan robustness was estimated.

Results: Analysis of 3D-printed compensators homogeneity allowed for plan range uncertainties estimations. Appropriate overwrite Hounsfield unit (HU) values were determined. Variations in compensator homogeneity altered its water equivalent ratio (WER) by not more than 3.5 % being within the limit for plan robustness evaluation. Usage of 3D-printed compensators showed higher conformity and resulted in better sparing of OARs. Appropriate placement of ball-bearing markers within compensator structure led to patient positioning errors similar to standardized procedures.

Conclusions: Application of 3D-printed compensators led to more conformal dose distribution as compared to RS placed at nozzle, which allowed to meet clinical objectives. Dedicated QA procedure permitted to keep the plan range uncertainty evaluation unaffected.

PTC58-0486

Fast neutron therapy treatment planning in RayStation

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High linear energy transfer (LET) fast neutron therapy is uniquely beneficial in the treatment of select cancers. At the University of Washington (UW), the Clinical Neutron Therapy System (CNTS) has been used to treat over 3,200 patients since 1984. To harmonize and improve the efficiency of treatment planning across modalities (MV x-rays, electrons, protons and fast neutrons) and enable the delivery of Intensity Modulated Neutron Therapy (IMNT), a neutron-specific beam model has been successfully implemented in a beta build of the RayStation 8 treatment planning system (TPS). The Monte Carlo (MCNP6) code system was used to generate scattering kernels for neutron energies relevant to the CNTS (1 keV to 51 MeV). Integration of the neutron kernels into the RayStation TPS is capable of matching measured depth-dose, lateral profiles, and output factors with almost a 100% pass rate using a 3%/3mm criteria for all square and wedged fields. (RayStation Benchmarking) Figure 1 shows the agreement between RayStation model and ionization chamber measurements (green=pass, red=fail) for a 28.8×32.8 cm^2 open field. Recalculation of a large number of patient treatment fields with the RayStation model are also in excellent agreement with measurements. The accuracy of the RayStation model is superior to past treatment planning options for the CNTS, reduces planning time from days to hours, and enables IMNT treatment planning, as illustrated in Figure 2. Figure 2 also shows the excellent agreement between a collapsed cone (point dose kernel) plan and singular value decomposition (pencil beam dose kernels) for a representative IMNT plan.

PTC58-0492

Fluence perturbations from fiducial markers due to edge-scattering effects measured with high resolution pixel sensors for 12C ion beams

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In particle therapy, a mispositiong of the patient can lead to severe underdoses in the tumor. Furthermore, displacements of the tumor (e.g. prostate cancer) can occur and cannot be seen by the daily positioning verification. Therefore, fiducial markers are used to precisely locate the tumor and verify its position. They are made of heavy materials in order to be visible on images (e.g. x-ray). However, they also lead to local over- and underdosage due to inhomogeneous scattering of the ions. This effect was already evaluated with MC simulations and film measurements. Here, for the first time fluence measurements were performed with high resolution pixel sensors to evaluate precisely the over- and undershoot in 3D. The measurements were done at the Marburger Ionenstrahl-Therapiezentrum with different ^{12}C beams for markers commercially available. Two sets of pixel sensors were placed before and after the marker positioned inside a water phantom. The trajectory of every particle can be reconstructed with a resolution better than 10 μm. By reconstructing the fluence map of all tracks (Figure1), the perturbations induced by the markers can be determined. Preliminary results of measured undershoots caused by the markers are shown in Table1. Corresponding FLUKA simulations were in good agreement with the measurements and showed that ZrO_2 markers could be a good alternative compared to gold markers.

PTC58-0523

Technical delivery parameters for 2000 spot scanned proton treatment courses over a three-year period

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There has been much discussion on what various technical parameters a proton delivery system should be capable of, for example field size and energy ranges. Presented are the technical delivery parameters for 2023 spot scanned treatment courses over a 39-month period. Some of the parameters explored include the maximum and minimum water equivalent thickness (WET) used per field, the maximum and minimum field size per field, the number of protons per field, the number of energy layers per field, the number of fields per plan, number of fractions per course and the gantry and table angles per field. These parameters were explored by aggregate and by treatment site. In aggregate, the median maximum field size was 12.4 cm, 95% of the fields had a maximum field size less than 28.7 cm, with a maximum field size of 39.8 cm. In aggregate, the median field WET was 16.4 cm, 95% of the fields had a maximum WET less than 26.4 cm, and the maximum WET was 32.4 cm. Note that the delivery system has a maximum field size of 40 cm and a minimum WET of 4 cm without the use of a range shifting device. The WET statistics above are the WET in the patient, i.e. a WET of 0 cm is possible. The average monitor unit per field was 117.4, where one monitor unit ranges from 400 to 900 million protons depending on energy. Time trends over the 39 months of these technical parameters are also explored.

Physics: Dose Calculation and Optimisation
PTC58-0067

Monte Carlo investigation of dose enhancement due to gold nanoparticles in particle beam therapy

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Purpose: We investigated the dose enhancement effect due to gold nanoparticles in particle beam (^{12}C, ^{4}He, proton) irradiation.

Methods: For Monte Carlo simulation, TOPAS version 3.1 patch 03 was used. Firstly, ^{12}C ion scanning beams of mono-energetic 283.33 MeV/u, ^{4}He ion scanning beams of mono-energetic 150 MeV/u, and proton 150 MeV were irradiated to a water-filled phantom ($30 \times 30 \times 30$ cm^3), and secondary particle information generated near the Bragg peak was recorded in a phase space file. Secondly, the obtained phase spaces file were squeezed to nanometer scale (50 nm) to irradiate gold and water nanoparticles of 50 nm diameter located at the center of $4 \times 4 \times 4$ μm^3 water filled cube phantom. Dose enhancement ratio (DER) was calculated with a 1 nm thickness of a concentric shell shaped detector placed up to 50 nm from the nanoparticle surface. The DER was computed at every 1 nm distance from the surface of the nanoparticle.

Results: Computed gold nanoparticle DER at 1 nm from the nanoparticle surface was 4.89, 4.86, and 4.69 results for proton, ^{4}He, ^{12}C particle beam respectively. There was no significant difference in DER depending on the particle beam, and it rapidly decreased from the gold nanoparticle surface.

Conclusion: Gold nanomaterials have the potential to be used as a radiosensitizer in particle beam therapy. When using gold nanoparticle in particle beam therapy, the dose enhancement effect of the gold nanoparticles absorbed within the tumor cell would be a delivery more therapeutic dose.

PTC58-0452

Benchmarking micro- and nanodosimetry spectra and free radicals simulated with GEANT4DNA, LQD, PHYCHEML, CHEM for ion beams

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Introduction: To optimize hadrontherapy treatments, the relative biological effectiveness (RBE) needs to be estimated through biophysical models. The Microdosimetric Kinetic Model (MKM) [1] and the Nanodosimetry Oxidative stress model (NanOx) [2] rely on the calculation of the specific energy spectra at nano- and micrometric scales. The NanOx model introduces also the concept of chemical specific energy based on the production of free radicals. This study proposes to benchmark GEANT4-DNA and LQD/PHYCHEML/CHEM specific energy and lineal energy spectra simulations and the yields of primary species induced by water radiolysis. Physical and chemical data are estimated for protons and carbon ions monoenergetic beams.

Material and Methods: The ion tracks in water are simulated using GEANT4-DNA. The three dimensions energy transfer points analyzed with the TED code is used to calculate the specific energy and the lineal energy spectra in micro and nanometric targets. Radiochemical products (e-aq, OH., H2O2., O2-.) are calculated with the chemistry module of GEANT4-DNA and with PHYCHEML and CHEM codes for LQD. Same quantities are then evaluated for SOBP through the superposition of monoenergetic ion tracks.

Results: The comparison of the results issued from GEANT4-DNA and LQD will be presented for monoenergetic beams. Results obtained for SOBP will also be shown. This study is preliminary to a full implementation of the MKM and NanOx models into the GATE platform.

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PTC58-0544

Evaluation of plan optimisation strategies to reduce proton PBS spot placement distal to the target in the presence of heterogeneities

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Purpose/Objective: Proton pencil beam scanning (PBS) treatment planning systems (TPS) define maximum beam range based on the Weq pathlength to the deepest plane. No spots are placed distal to the target when planning in homogeneous media, but they are when heterogeneities are introduced.

Aim of this study is to evaluate optimization strategies to minimize this effect.

Materials and Methods: Calculations were performed using Eclipse v13.5. Within a (40x40x40)cm^3 water phantom a (5x5x5)cm^3 target was created with proximal surface at 10cm Weq depth. Within the target, bone and air equivalent structures were created, both (2x2x2)cm^3. Calculation grid was 2.5mm; densities set to 1000, -1000, and 0 HU for bone, air, and water respectively. Plans to target+5mm 3D margin were calculated and optimized on target only to deliver homogeneous dose (min 100%, max 102%).

Nominal plans were re-optimised using the following strategies: minimum spot weights varied between 0.021–0.11; normal tissue objective (NTO) default setup (98 to 80% in 0.43cm), and adjusted setup (80 to 20% in 0.43cm), each with various optimization weights (10-100%); zero dose to 'ring1′ (5mm distal to target), and to 'ring2′ (2.5mm distal to target), each with various optimization weights (10-100%). All plans optimised using nonlinear universal proton optimizer (NUPO). Plans were compared.

Conclusions: Rings reduced number of spots beyond the target. NTO improved lateral penumbrae. To balance target coverage with spot reduction distal to target we recommend using a ring 2.5-5.0mm distally with up-to 50% target optimization weight applied. Manual removal of spots may still be required.

PTC58-0025

Comparison of PENH, FLUKA and Geant4/TOPAS for ionization chamber calculations in proton beams

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Purpose/Objective: This works compares the performance of the Monte Carlo codes PENH, FLUKA and Geant4/TOPAS in the calculation of beam quality correction factors in proton beams.

Material/Methods: The absorbed dose to water (*D*w) in a reference volume in a water phantom as well as the absorbed doses in two air cavities (*D*air) representing cylindrical and plane-parallel ionization chambers were calculated with the Monte Carlo codes PENH, FLUKA and Geant4/TOPAS for the beam qualities *Q0* (1.25 MeV mono-energetic photons) and *Q* (150 MeV protons). Additionally, EGS as a commonly used Monte Carlo code for photon simulations was used to calculate *D*w and *D*air in the photon beam. Subsequently, the ratios $fQ=(D\mathrm{w}/D\mathrm{air})Q$ and *fQ/fQ0* were calculated. *fQ/fQ0* is the basis of beam quality correction factors.

Results: In Figure 1 the dose values in the cavities for both beam qualities (panel (a) for photons, panel (b) for protons) are shown. In the bottom panel the deviations relative to PENH are shown. For the photon irradiation the deviations between the codes are 1.4% at maximum whereas for the proton irradiation the deviations are 1% at maximum. In Figure 2 the ratios *fQ/fQ0* for the two air cavities are shown. The results agree within two standard deviations or better. The maximum deviation is 0.6%.

Conclusion: It was shown that by using appropriate transport settings the results of the *fQ/fQ0*-ratios agree within 0.6% between the Monte Carlo codes. In other words, PENH, FLUKA and Geant4/TOPAS are suitable to calculate *fQ/fQ0*-ratios in proton beams.

PTC58-0026

Analysing the effects of the Bragg peak degradation due to lung tissue in proton therapy of lung cancer patients

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Purpose and Objective: Sub-millimetre-sized heterogeneities like lung tissue cause a Bragg peak degradation. If not considered in treatment planning this can significantly influence the dose distribution in lung cancer patients. In a previous study we presented a strategy to consider this Bragg peak degradation. In this study we use this tool to analyse the effects on treatment plans of patients.

Material and Methods: Stereotactic treatment plans of five different lung cancer patients (tumors of sizes 2.7-46.4 cm3 at depths of 1.8-12.2 cm) were optimised for protons using ECLIPSE (VARIAN). These treatment plans were then recalculated using the MC-toolkit TOPAS while reproducing the Bragg peak degradation due to the lung tissue to gain the actual dose distribution in the patient.

Results: In Figure 1 the 90% isodose is shown for the dose prediction from ECLIPSE (purple) and the dose distribution in the patient (green) indicating the underdose of the CTV (white). In Table 1 the relative underdose of the CTV in terms of the mean dose D*mean*, D98% and D2% for the different patients are shown. The underdose of the CTV is about 5% at maximum. Using the geometrical information, we could show that the effects increase with an increasing depth of the tumor in the lung and with a decreasing volume of the target.

Conclusion: This is the first study to investigate the effects of the Bragg peak degradation due to lung tissue on lung cancer treatment plans in proton therapy. The maximum effect on the mean dose in the CTV was roughly 5%.

PTC58-0444

Performance tuning and integration of a Monte Carlo-based and GPU-accelerated robust optimization system for Intensity Modulated Proton Therapy

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Purpose: To tune the performance, integrate, and test a Monte-Carlo-based robust optimization system for IMPT on a high-performance GPU-cluster for clinical use.

Methods: Using an in-house GPU-based MC dose engine and robust optimizer, we built a complete robust optimization system for IMPT for clinical use that runs on a multi-node and multi-GPU high performance cluster. Computational bottlenecks of the optimizer were first identified and removed. In particular, regarding data localization on the GPUs and using efficient CUDA libraries. The Monte Carlo dose engine was also expanded to run on multiple GPUs using Message Passing Interface (MPI). Various components of the system are parallelized when possible. Both physical and LET based biological dose optimizations are included.

Results: The system was tested on a high-performance cluster with 42 nodes, each with 4 Tesla K80 GPUs. Small cases take ~15 minutes while large bi-lateral head and neck takes ~60 minutes. Dose calculation and optimization are 55% and 30% of the total time, respectively. In Figure 1, we show the computational work flow. In Figure 2, we show timing for various patient cases as well as scaling with the number of computational nodes.

Conclusions: We built and tested a clinically applicable robust optimization system capable of biological dose calculation for IMPT based on Monte Carlo dose engine. The system is interfaced with the treatment planning system. Although the current timings are clinically viable, further improvements are still possible which will reduce the computational time.

PTC58-0315

TRAX-CHEM: A new tool for unraveling chemical stage related issues in ion beam tracks

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A new platform simulating the radical production and diffusion and recombination in particle tracks has been developed extending the TRAX code. The recent implementation together with some possible advanced features achievable with it is here presented with a special focus on possible nanoscopic mechanisms underlying the hypoxia radiosensitization with particle beams.

After including the pre-chemical and chemical stages of the radiation effect through a Monte Carlo step-by-step method, the validity of the model has been verified by comparing the calculated time- and LET-dependent yields of the different radiolytic species to the available experimental data and other simulation approaches. Simulation possibilities now include the chemical evolution of the most important products of water radiolysis under different irradiation conditions and target oxygenation levels. Accordingly, differential radical recombination and final (1μs) yields for different oxygenations are presented to elucidate the molecular mechanisms that contribute crucially to the indirect effect on biological systems.

The updated model also promises to aid the basic understanding of damage mechanisms in other complex scenarios such as nanoparticle sensitization and the role of radical scavengers on the chemical kinetic along an ion track.

PTC58-0015

Measurement of the stopping power of liquid water for carbon ions below 6 MeV

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The stopping power of water for carbon ions (SH2O,C) is a crucial parameter to determine the range of projectiles in human tissue. It is evident that a precise knowledge of this quantity reduces (part of) the range uncertainty which allows to avoid energy deposition in the healthy tissue as well as critical organs placed behind the target volume. In addition, experimental data for carbon ions as tabulated by the PIDE Project indicates an increasing relative biological effectiveness (RBE10) for linear energy transfers (LET) prevailing in the Bragg peak of water, see Figure. In the context of therapy planning, this increased effectiveness can only be incorporated if the LET is known with sufficient accuracy. However, experimental data for SH2O,C at such low projectile energies is sparse.

In the present work, we applied the Inverted Doppler-shift Attenuation Method to the decay of the 2+ state at 4.4 MeV ($\tau = 61$ fs) in 12C to measure SH2O,C for projectiles with kinetic energies below 6 MeV. The experimental data is analyzed by comparison to spectra generated with a dedicated Monte-Carlo simulation. Results of a first experimental run using a provisional experimental setup agree with the recommendation of the ICRU report 73 errata and recent theoretical results, but the experimental uncertainty of 12% is comparably large. We will present preliminary results of measurements performed with the full experimental setup. In addition, we will provide first information on a follow-up experiment in which we aim to quantify the mean ionization potential $<I>$ of liquid water.

PTC58-0032

Detecting prompt gammas as a means of dosimetry and range verification measurements for treatment validation of high-energy beams in PBT

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When proton beams of therapeutic energies interact with tissue, a variety of nuclear interactions ensue. Prompt gammas are one of the secondary products produced as a result of such interactions. Through Compton Imaging, spatial and energy information can be obtained in order to reconstruct the paths of the prompt gammas and determine the point of interaction where they were produced. In turn, this enables spatial information about the dose deposition to be determined. We propose the implementation of a three-tiered Compton Camera system to detect prompt gammas and employ this Compton Imaging technique in order to compute dosimetry and range measurements for high energy clinical proton beams. This implementation of Compton Imaging seeks to enhance the precision with which we can characterise the internal trajectory of protons, hence improving the targeting of Proton Therapy. Our work provides a non-invasive treatment validation technique which allows for live time measurements.

The goal of this presentation is to discuss experimental results from our 'portable' three-tier CC system and the development of a Geant4 simulation developed to verify our system.

PTC58-0072

Quantifying robustness and calculating the probability of meaningful error in proton radiotherapy delivery utilizing a dense D_{ij} matrix

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When conventional intensity modulated proton therapy algorithms calculate optimal beam spot weights, there is no formal consideration of potential systematic errors. Alternatively, robust optimization addresses these uncertainties within its objective function, yielding plans that are less subject to dose fluctuations when errors occur. Despite these advances, quantifying plan "robustness" remains challenging and clinicians have little guidance regarding the likelihood that a plan fails to meet constraints.

We describe a novel method of quantifying robustness, yielding a nonparametric probabilistic approximation of dose coverage. Rather than creating a D_{ij}matrix limited to those beam spots (BS) intended for use in treatment delivery, we propose creating a "dense" D_{ij}matrix (DDM) with finer spot spacing (1 mm X/Y-axis, 0.6 MeV E-axis) and wider margins (2.5σ). Simulations indicate that DDM calculation is feasible with file sizes ranging 50-75 times that of primary Dij matrices.

Following optimization, 100 error scenarios are created by translating the optimized plan with normal random shifts in the X,Y, and Energy axes, corresponding to the known uncertainty distributions in these respective dimensions. Since the locations of BS in each error scenario closely approximate locations of BS already included in the DDM, dose calculation of all error scenarios is completed with minimal additional computation. Review of a composite DVH comprised of all simulated error plans allows one to quickly measure robustness (spread of DVH distributions) and determine the fraction of error scenarios that fail to meet constraints, thus allowing clinicians to provide safer and more effective treatments.

PTC58-0529

Experimental validation of a commercial Monte Carlo treatment planning system for proton uniform scanning fields including aperture and range compensator

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Introduction: A commercial Monte Carlo (MC) treatment planning system (TPS) for proton uniform scanning (US) fields was tested with measurements in water equivalent and Alderson-Rando (AR) head and neck phantoms.

Methods: Proton US fields were generated in a research build of the commercial TPS RayStation (v7.120) with different nozzle settings (ranges: 10-25 cm, modulations: 5-10 cm) and a clinically realistic aperture and compensator. Depth-dose curves were calculated using the MC dose engine (v4.2) and compared with multi-layer ionization chamber (MLIC) measurements. A US field using an oblique beam angle was planned and delivered to an AR phantom. Four planar doses calculated by MC and pencil beam convolution (PBC) dose engines were compared with the GafChromic™ film measurements using the One-scan protocol (Lewis et al., Med Phys. 2012).

Results: The depth-dose curves calculated by the MC dose engine in water agreed with MLIC measurements within 1.5% dosimetrically and 1 mm in range (Figure 1). The planar doses calculated by the MC dose engine in the heterogeneous AR phantom demonstrated significantly better agreement at the bony structures around the field entrance and distal-dose fall offs, and air cavities around the spread-out Bragg peak (SOBP) (Figure 2). The average Gamma passing rates (absolute DD: 3%, DTA: 3mm) were 97.1% (range: 95.1%-98.4%) and 91.6% (range: 88.1%-94.1%) for the MC and PBC planar dose calculations compared with the film measurements respectively.

Conclusions: The new MC dose engine has been validated by both chamber and film measurements and improves dosimetric accuracy significantly in the heterogeneities.

PTC58-0605

Comparison of pencil beam and Monte Carlo algorithms in spot scanning proton therapy: A retrospective analysis of patient-specific QA measurements failure

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Purpose: To evaluate the accuracy and understand the model deficiency of pencil beam and Monte Carlo algorithms in proton spot scanning dose calculation, benchmark against the patient-specific quality assurance (PSQA) measurements.

Materials and Methods: Dose distributions in homogeneous water phantom from patient treatment plan were verified by MatriXX measurements for PSQA. Among 893 treatment plans verified during 2016.11-2018.6, 37 plans failed to meet the acceptance criteria were re-calculated by an in-house developed Monte Carlo-based fast dose calculator (FDC). Outcomes of 329 dose plane measurements were retrospectively reviewed. Central axis point dose variations relative to measurement were compared between Eclipse pencil beam algorithm (PBA) and FDC, as were the planar dose distributions quantified by 3%/3mm gamma passing rate.

Results: The FDC showed substantially improved agreement with measurements in point dose variation (-0.55±4.19% to -5.14±6.70%, $p<0.001$) and gamma passing rate (97.48±4.48% to 89.12±13.17%, $p<0.001$). PBA severely underestimated the point dose in the proximal (5.35±2.71%, FDC: 3.16±1.63%) and distal regions (12.33±9.86%, FDC: 2.01+7.15%), and the gamma passing rates decreased to 82.44±14.97%(FDC: 98.92±1.23%) and 79.17±11.23%(FDC: 97.06±5.46%.). For fields using range shifter and aperture, maximum point dose discrepancy of FDC reached 33.31% and gamma passing rate dropped to 73.2%.

Conclusions: FDC significantly reduced point dose discrepancy and improved planar dose gamma passing rate against PSQA measurement in the proximal and distal region. Inherent deficiency of low-dose envelope modeling in Eclipse PBA could not be compensated by additional single-spot fluence modelling. Further study was required to validate the accuracy of the range shifter and aperture modeling in FDC.

PTC58-0583

Independent dose calculation for non-isocentric scanned proton treatments using GATE/Geant4

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Introduction: For highly complex treatments using pencil beam scanning as implemented at the MedAustron Ion Threapy Center (Wiener Neustadt, Austria) it is of paramount importance to perform a dosimetric plan verification before each treatment. However, the patient-specific plan verification requires precious beam time that could be used for treatment or further commissioning. In this respect, Monte Carlo simulations can provide an alternative for the validation of dose calculations performed by the Treatment Planning System (TPS) and speed up the verification procedures.

Material and Methods: Clinical cases such as clival chordoma, para-nasal carcinoma and prostate carcinoma were selected. The use of a range shifter as well as reduced air gap between treatment head and water phantom surface (non-isocentric condition) were taken into account in the simulations. Analysis was performed in terms of local dose deviations to measured data. A gamma index analysis of 1mm/1% as well as 2mm/2% was performed between GATE (GATE-RTion v1.0) and TPS (RayStation v6.1).

Results: GATE showed an average agreement to measured data of -0.6%±1.5%. A very similar trend was obtained with the TPS (figure 1). A systematic deviation of -1.5%±1.1% was found for both TPS and GATE when a range shifter was used. On average, the gamma pass-rate between GATE and TPS was found 85.7% and 98.1% at 1mm/1% and 2mm/2%, respectively.

Conclusion: GATE represents a validated tool for supporting the plan verification re-calculation and it will be clinically implemented in 2019 as part of patient specific quality assurance procedure at MedAustron.

PTC58-0020

Dependencies of the Bragg peak degradation in lung for proton therapy based on phantom studies

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The fine, sub-millimeter sized structure of lung causes a degradation of the Bragg peak curve in particle therapy. Since this fine structure of lung tissue is not resolved in treatment-planning CTs, current state-of-the-art dose calculation procedures are unable to account for this degradation. This can lead to an underdose in the target volume in general and an overdose distal to the target.

Proton plans were optimized on geometrical CTVs in CT-based phantoms and afterwards recalculated with the TOPAS Monte Carlo code: without consideration of the degradation and with the Bragg peak degradation accounted for [1]. Various changes in parameters that could influence the Bragg peak degradation, such as tumor size and shape or the depth in lung were simulated to quantify the effect on the dose distribution.

Figure 1 shows an exemplary depth dose curve with and without the Bragg peak degradation. Figure 2 gives the reduction of the mean dose in dependency of the depth in lung for different tumor volumes. The results show that due to the degradation the mean dose in the target volume can be reduced by a few percent up to 8% depending on the geometry. This effect increases with a decreasing tumor volume and increasing depth in lung. [1] Baumann et al. An efficient method to predict and include Bragg curve degradation due to lung-equivalent materials in Monte Carlo codes by applying a density modulation Phys. Med. Biol.

PTC58-0601

Multi-field optimization (MFO) compared to single-field optimization (SFO) for bilateral head and neck cancer

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Introduction: Multi-field optimization (MFO) offers dosimetric advantage for highly conformal plan compared to Single-field optimization (SFO) but is more susceptible to range and setup uncertainties, especially in bilateral head and neck cancer where target volumes are relatively complex surrounding with organs at risk (OARs). This study compares SFO with MFO and we report our findings.

Methods: Five patients previously treated with bilateral head and neck cancer with SFO and Monte Carlo dose calculation were retrospectively re-optimized with MFO. All patients were treated to a prescribed dose of 69.96 Gy(RBE) in 33 fractions with 3-4 dose levels to lower risk disease using a 3-field arrangement. All target volumes were optimized with 3mm geometric uncertainty to ensure plan robustness. Treatment plans were evaluated with 3% range uncertainty and 3mm geometrical shifts in each direction. Target coverage and dosage to OARs were compared between SFO and MFO technique.

Results: MFO generally yielded similar D98 and D2 values for target coverage against SFO with average difference of 0.45% and 0.82% respectively. Mean dose to OARs was between 2.67 and 8.05 Gy(RBE) lower with MFO. No significant difference in robustness analysis for target coverage was shown between SFO and MFO, with 1.01% and 1.68% higher in range and setup uncertainty respectively for MFO. Variations to dosage in OARs were comparable, with 3.23 Gy(RBE) higher in maximum dose to spinal cord in worst-case scenario.

Conclusions: MFO with robustness improves dose distribution over SFO and is within acceptable plan robustness in bilateral head and neck cancer.

PTC58-0635

Consideration of the Bragg peak detector size in the modeling of proton PBS machines in the treatment planning system RayStation

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Two sets of single spot integrated depth doses (IDDs) in the energy range 100-226 MeV were recorded using the IBA dedicated PBS nozzle in Gantry treatment room 4 of the West German Proton Therapy Center in Essen (WPE). The first set used the Bragg Peak Chamber® detector (BPC) from PTW, which has an electrode diameter of 81.6 mm. The other set of IDDs were recorded using the significantly larger StingRay® detector from IBA dosimetry, with a diameter of 120 mm. In addition, central axis depth dose curves (DDCs) of 10.25x10.25 cm^2 scanned fields in water were measured. Based on the two sets of measured IDDs, with their corresponding detector diameter as input, two beam models were created in the treatment planning system RayStation (v.8A), and DDCs corresponding to the measured DDCs were then calculated for each of the models.

Excluding the high gradient parts around the Bragg peak, the relative difference between the measured IDDs of the two detectors was found to be up to 2.8%, with the largest differences at intermediate depths for the highest energies. However, the relative difference between the measured and the two sets of calculated DDCs were within 1% and was dominated by random noise from the measurements. No systematic dependence in depth, energy, or type of detector was found. This shows that the lateral extension of the IDD detector is accurately considered in the RayStation beam modeling and that the same degree of accuracy can be achieved using either of the BPC or StingRay® detectors.

PTC58-0234

Pareto based beam orientation optimization method for intensity modulated beam proton therapy

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Purpose: Provide a novel multicriteria Pareto based method for beam orientation optimization for IMPT implemented on a multi-GPU computing system.

Methods: A novel beam orientation multicriteria optimization algorithm based on differential evolution (DE) was implemented. The algorithm explores all the feasible (4Pi) space for a given number of fields. For every set of angles dose calculation was performed using Monte Carlo code, the proton beam spot intensities were optimized using a GPU iterative optimizer. The DE algorithm was implemented to work in parallel on a multi-node multi-GPU cluster. The Pareto based beam angle optimization algorithm was validated on two brain tumor cases. The performance of the plans was gauged on the following DVH based objectives; 1) deviation of the target coverage at the 98% volume and 2) dose deviation of organs at risk at 50% and 1% volume points. A comparison study to a manually selected set of beam angles was performed.

Results: The beam angle optimization algorithm generated Pareto surface for the two brain tumor cases. The algorithm provided the Pareto database and was able to find beam angles which performed equivalent to or better than normal tissue sparing for the manually selected angles. The D[1%] dose sparing for the first case showed up to 6-8 Gy reduction in dose compared to manually selected angles, and up to 4-30 Gy in the second case.

Conclusion: Pareto based beam angle optimization algorithm was used to automatically generate the Pareto database and provide a high quality plans with minimal human interaction.

PTC58-0170

The complementary methods for reduction of the dosimetric impact from scattered protons in the passive scattering proton therapy

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Purpose: In this study, the complementary methods which can be applied with the current TPS is suggested for reduction of the dosimetric impact from scattered protons in the passive scattering proton therapy

Methods: To reduce the additional dose from scattered protons, which is not expected in the treatment plan, both methods using the thicker compensator base and bolus were applied. For the same target volume on the solid water phantom, treatment plans were established with the compensator bases and bolus of different thickness. The results from measurement, TPS calculation, and MC simulation were compared for the verification of effectiveness of both methods. The MLIC (multi-layered ionization chambers), radiochromic films, and MatriXX were used for this measurement.

Results: The measured results show that the additional dose from scattered protons was reduced in the both suggested methods. The measured dose was in agreement with the calculated dose from the MC simulation, and also had less difference with the TPS calculation. As expected, the difference due to the additional dose from scattered protons was reduced with the thickness of compensator base and bolus in the measurement and MC simulation.

Conclusions: In this study, the complementary methods to reduce the additional dose from scattered protons were suggested and their effectiveness was verified. With the both methods using the thicker range compensator bases and bolus, the additional dose was reduced in the measurement so that the less difference is shown between measurement, MC simulation, and TPS calculation.

PTC58-0134

Stochastic RBE in CNS clinical SOBP: A novel approach

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Proton Relative Biological Effectiveness (RBE) has been widely studied to model biological effects in treatment planning. In most proton centers, RBE is recognized as a constant value of 1.1, while a few other centers have developed their own model to determine the proton RBE. Most studies have shown that proton RBE varies with proton dose (D_p), α/β ratio and linear energy transfer (LET). In this work, we will quantify the uncertainties of RBE weighted dose in Spread Out Bragg Peak (SOBP) by using a novel stochastic RBE approach, where RBE is a *random variable*. A Gaussian model is used to sample the RBE This approach allows us to analyse the uncertainties of RBE weighted dose within each individual voxel in the volume of interest and take these uncertainties into consideration during treatment planning. Dose calculation and sampling of RBE were done using Monte Carlo simulation with GEANT4 in a homogeneous phantom and a clinical Central Nervous System (CNS) patient. A SOBP with the variation of RBE weighted dose was then evaluated using MATLAB in both examples. In conclusion, the preliminary result of this work has enabled us to quantify the significance of biological uncertainties for proton treatment planning.

PTC58-0140

A novel hybrid model for out-of-field dose calculation in proton therapy treatment planning

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One of the main rationales of proton therapy is the lower exit dose, resulting in reduced dose to healthy tissue distal to the treatment volume and increased organ sparing. However, high energy protons produce neutrons in the treatment head and in the patient that can distribute dose well outside the treatment field. The variable biological effectiveness of neutrons along with the current inability of treatment planning systems (TPS) to account for out-of-field dose means that there is a gap in knowledge and documentation regarding the potential risk of developing a second cancer for patients undergoing proton therapy.

Computational phantoms provide one way of calculating the dose within a patient for a given treatment plan. A new polygon mesh computational phantom was here adopted for scaling to match individual patient measurements and treatment positions. By combining computed tomography data representing the in-field and a customized computational phantom derived from the mesh phantom covering the out-of-field, we aim to improve estimates of neutron dose in far field organs of interest accumulated during proton therapy. This computational framework has been integrated in Geant4 for coupling to an in-house TPS research engine. The Monte Carlo-based dose estimation in a more realistic whole-body patient anatomy will eventually be coupled to various risk models to estimate the risk of secondary cancer due to the therapy, and this in turn will be used to further optimize treatment planning. Initial results of the project, including validation of the proposed methodology, will be presented. Funding: DFG Graduiertenkolleg 2274

PTC58-0360

Implementation and commissioning of the FRoG framework at the Danish Center for Particle Therapy

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The Danish Center for Particle Therapy (DCPT) will treat its first patient soon. To facilitate a rapid and robust dose calculation that also functions as an independent secondary dose calculation, Fast dose Recalculation on GPU (FRoG), has been implemented at DCPT. FRoG, which has been developed in-house at the Heidelberg Ion Therapy Center (HIT) and the Centro Nazionale di Adroterapia Oncologica (CNAO), has previously shown excellent agreement with both gold standard Monte Carlo (MC) simulations and measurements due to its superior beam splitting algorithm and triple Gaussian beam model. CNAO and HIT are both synchrotron-based facilities whereas the DCPT uses a cyclotron and beam delivery provided by Varian Medical Systems. Minor adjustments in the codebase had to be made to enable FRoG at DCPT. Furthermore, DCPTs beam shape and integrated depth dose distributions (iDDDs) were modelled in FLUKA MC to generate LET and iDDD distributions for FRoG base data. Figure 1 shows FLUKA-generated iDDDs against measurements at DCPT, demonstrating excellent agreement. Continuous energy selection used at DCPT was implemented by means of Bragg Peak interpolation between commissioned iDDDs. Initial validation studies show good agreement between measurements and FRoG predictions. Extensive validations against measurements and the clinically used treatment planning system of DCPT (Eclipse, Varian Medical Systems, Palo Alto, CA, USA) are currently underway. With the FRoG framework, comprehensive large-scale studies on plan robustness, dose delivery and biological effect can be performed at DCPT within a clinically reasonable time-frame due to FRoGs extensive GPU utilization and flexible dose engine.

PTC58-0376

Multi-ion biological and physical dose optimization with the FRoG framework

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By 2020, the Heidelberg Ion-beam therapy Center (HIT) will treat patients using three unique particle beams: proton, helium and carbon ion beams. The addition of helium ions adds flexibility to clinical decision-making to yield more favourable dose distributions. To facilitate fast and accurate dose comparisons for the three ions, Fast dose Recalculation on GPU (FRoG) has been developed. FRoG affords both physical and biological dose calculations within minutes and demonstrates excellent agreement with the gold standard Monte Carlo (MC). To support the clinical workflow and enable extensive biological studies, the FRoG engine has been extended with a dose optimization algorithm that supports SFUD and IMPT optimization and the usage of multiple biological models.

As a feasibility study, helium and multi ion plans have been optimized for varying rectangular field sizes and doses from 3 to 5 GyRBE. A data-driven model of relative biological effectiveness (RBE) for helium ions was recently published in A. Mairani et al., whereas the local effect model was used for multi-ion plans. The optimization parameters were set to provide a nearly constant RBE in the target (Fig. 1).

MC simulations were performed and showed good agreement with the FRoG plans. In addition, the plans are going to be delivered at HIT on a cell line with $\alpha/\beta=2$ to investigate the cell survival. The experimental results will be used to verify current biological models for helium and multi-ion irradiation. With this work, FRoG is an integral part of the clinical and experimental workflow at HIT.

PTC58-0146

We are developing a containerized Monte Carlo dose calculation engine integrated with CPU and GPU accelerated algorithms

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Monte Carlo simulation is often employed to derive precise dose calculation results for radiotherapy due to its ability to simulate complex physics interactions between incident beams and irradiated subjects. However, applying Monte Carlo simulation to clinical practices poses a significant challenge because of a huge amount of computational demands and time. In response to this challenge, an in-house dose calculation engine using the condensed history class-II Monte Carlo method is developed with various CPU and GPU accelerated algorithms. Moreover, we adopt the latest container framework, docker, for the ease to deploy the accelerated in-house dose calculation engine onto different acceleration platforms, such as a PC equipped with an NVIDIA GTX 1080 GPU card or a server equipped with hundreds of CPU cores. At the moment, we focus on proton therapy simulation. The physics simulations include electromagnetic processes, such as continuous ionization, energy straggling, and multiple coulomb scattering by Highland's approximation, while the processes via the nuclear forces for elastic and non-elastic scattering are in progress. A typical test example of 160-MeV proton beam into water is presented for comparing the simulation time and results between single-threaded Geant4-10.5.0 and the developed GPU algorithm of our in-house dose calculation engine executed on the platforms, each of which is equipped with NVIDIA GTX 1060 and GTX 1080 GPU cards, respectively. Comparing with the dose simulation results of Geant4, the passing rates of 1%/1mm gamma index achieve 100% and the speedup factors are 104 and 221 times, respectively.

PTC58-0337

A Monte Carlo model of proton spot scanning for dose reconstruction of pediatric patients for epidemiological studies of late effects

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The International Pediatric Proton Therapy Consortium (IPPTC) has been launched to initiate large-scale collaborative research on late health effects in children following proton therapy. As a groundwork dosimetry effort for this project, we established a Monte Carlo (MC) model of proton spot scanning beams to estimate organ/tissue doses of pediatric patients at the Maryland Proton Treatment Center (MPTC), one of the proton centers involved in the IPPTC. The MC beam modeling was performed using the TOPAS code. The spot parameters (mean energy, energy spread, spot size, and spot divergence) as a function of the nominal energy were determined by matching the MPTC beam commissioning data (integral depth doses and spot profiles). An in-house program was developed to automatically generate a TOPAS parameter file that implements spot information planned by the MPTC treatment planning system (TPS). The established MC model was then tested by calculating organ/tissue doses for brain-tumor and craniospinal irradiations planned on the 1- and 5-year-old ICRP reference phantoms. The calculated dose distributions in the PTV were compared with the TPS dose distributions (see Figure 1), showing the 3mm/3% gamma index passing rates of 99–94%, validating the MC model. The calculated organ/tissue dose equivalents for the craniospinal irradiations, as expected, were generally much higher than those for the brain-tumor irradiations (see Figure 2). In the future, the established MC model will be used to reconstruct organ/tissue doses for MPTC pediatric patients as well as be extended for patient dose reconstructions at other proton centers in the IPPTC.

PTC58-0398

Deriving Zeff for tissue characterization using the dual-energy computed tomography (DECT) technique and two commercially available CT phantoms

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Purpose: For Monte Carlo dose calculation in heterogeneous media, effective atomic number (Z_{eff}) derived from dual-energy CT images can be used for tissue segmentation. In previous studies, Landry (Phys. Med. Biol., 58, 6851 (2013)) and Saito (Med. Phys., 44, 2293 (2017)) performed Z_{eff} calibration on Gammex RMI 467 and CIRS 062M phantoms using selective limited rods. In this work, we extended the calibrations using all available rods. In-house Matlab codes were generated to automatize the process.

Materials and Methods: 13 and 16 material rods of the CIRS 062M and Gammex RMI 467 phantoms respectively were scanned on a GE RT590 CT machine using both 80 and 140 kVp x-ray beam energies. In-house Matlab codes following the methodologies of Saito and Landry were written and validated using their published data. Calibration curves of Z_{eff} vs. HU were obtained from scanning CT images of the rod materials by applying the in-house Matlab codes.

Results and Discussions: For HU converting to Z_{eff}, both methods from Saito and Landry were evaluated. Evaluation results on the CIRS 062M phantom showed largest/(mean$\pm$1 sigma) relative differences of (a) 37.4%/(5.4$\pm$9.3%) and (b) 5.7%/(0$\pm$2.4%) for Lung-inhale following Saito and Landry respectively. Similar evaluation on the Gammex RMI 467 phantom demonstrated largest relative difference of (c) 42.6%/(3.5$\pm$11.1%) and (d) 57.4%/(1.4$\pm$15.5%) for LN-300. Regardless of the evaluation types, the largest differences occurred at low density rods (Lung-inhale & LN-300). If removing the two outliers, (a)(b)(c)(d) become 17.0%/(3.5$\pm$4.7%), 5.7%/(0$\pm$2.4%), 14.0%/(0.9$\pm$4.2%), 11.5%/(0$\pm$4.1%), respectively.

PTC58-0595

Verification of pencil beam dose calculation in tissues of a MATLAB-based proton therapy treatment planning system

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The increased interest in application of proton therapy for cancer treatment has propelled research and education in this filed worldwide. Computational tools such as treatment planning systems and Monte Carlo simulations are useful for both physics and clinical studies. Recently, a MATLAB-based Proton pencil beam Scanning treatment PLANning system, so-called PSPLAN, has been developed for research and education. The dose calculation engine used in PSPLAN is based on the pencil beam algorithm, for which the 3D dose distribution is computed from the product of the depth dose distribution and the lateral dose profile. The depth dose distribution in tissues is related to dose in water by the water-equivalent path length using voxel-by-voxel CT numbers and ratios of stopping power of tissues to that of water. The lateral dose profile calculation in PSPLAN also takes into account tissue inhomogeneity off the central axis. In homogenous media the lateral dose profile is assumed to have a Gaussian distribution while in heterogeneous media the lateral profile of dose deviates from the Gaussian distribution according to the water equivalent distance to the central beam axis. Verification of the pencil beam dose calculation method used in PSPLAN is verified with PHITS Monte Carlo simulation using actual tissue inhomogeneity obtained from patient CT images.

PTC58-0065

Dosimetric and radiobiological impact of dose calculation algorithms on intensity modulated proton therapy for breast cancer

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Purpose: To evaluate the dosimetric and radiobiological impact of PB algorithm versus MC algorithm in intensity-modulated proton therapy (IMPT) plans for breast cancer treatment.

Methods: Twenty breast cancer patients who received IMPT to the breast/chest wall and regional lymphatics were included in this study. For each patient, 2 IMPT plans were generated: a PB-optimized plan and a MC-optimized plan. The radiobiological and dosimetric impact of the dose algorithms was assessed. The Poisson Linear-Quadratic model was used to estimate the tumor control probability (TCP). The influence of the model parameter uncertainties on the TCP was tested against different sets of published model parameters.

Results: The PB-optimized plans significantly underdosed the target as compared to the MC-optimized plans. The median (range) differences in CTV D95% and CTV Dmean were 3.8% (2.4% - 6.2%) and 2.4% (1.0% - 3.8%) of the prescription dose. The TCP was lower in the PB-optimized plans than the MC-optimized plans. The median (range) of the TCP differences (ΔTCP) were 4% (2% - 6%), 3% (2% - 5%), and 2% (1% - 3%), respectively, when calculated using 3 different model parameter sets. The ΔTCP correlated with the CTV dose difference, and moderately correlated with the CTV volume.

Conclusion: Due to the inaccurate dose modeling, PB-optimized plans under-dose the target and therefore yield a lower TCP compared to MC-optimized plans in breast IMPT. The magnitude of the resulting difference in TCP reached 6% in our study.

PTC58-0485

A golden beam data commissioning framework of Monte Carlo dose calculation algorithms of two pencil beam scanning treatment planning systems

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Purpose: Golden beam data (GBD) can potentially shorten commissioning time and minimize errors. However, there is no guidance on how to commission Monte Carlo Dose Calculation (MCDC) algorithms for Pencil Beam Scanning (PBS) using GBD.

Methods: A GBD framework was developed to commission MCDC algorithms of RayStation 8A and Eclipse AcurosPT v13.7.20 in water and heterogeneous phantoms. Measurements included Bragg peaks and profiles of PBS single-spots and PBS field outputs for Varian ProBeam. The phase parameters, numbers of protons per MU were obtained from in-air measurement and PBS outputs of 100 cm2 square fields at 2 cm depth, while spot profiles and more PBS fields at more depths were used to validate TPS.

Results: The maximum differences of phase parameters spot sigma and divergence between MCDC algorithms are below 4 μm and 0.26 mrad in air, respectively. Comparing TPS to measurement at depths, both MC algorithms predict the spot sigma within 0.5 mm, the resolution of measurement device. AcurosPT is found to underestimate numbers of protons per MU by $\sim$2% and requires user adjustment to match measurement, while RayStation is within 1% of measurement using Auto model. Site-specific gamma criteria vary from 2 mm/2% to 5 mm/5% with comparing TPS to exit dose measurement.

Conclusion: The proposed GBD framework can detect potential issues during PBS beam data collection or TPS commissioning processes. Therefore, it can shorten commissioning time and improve dosimetric accuracies. Secondary MCDC can be used to identify the root sources of disagreement between primary MCDC and measurement.

PTC58-0491

Pseudo proton radiography beam validation of Monte Carlo dose calculation in RayStation and Eclipse

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Purpose: To validate Monte Carlo Dose Calculation (MCDC) in heterogeneous media, one must ensure accurate calculation of proton range, absolute dose, and modeling of scattering properties. We investigated the feasibility using pseudo proton radiography beams through an anthropomorphic phantom to validate the newly released MCDC in RayStation and Eclipse treatment planning systems (TPS).

Methods: Stoichiometric calibration of CT Hounsfield Unit versus mass density was used in Raystation 8A and Eclipse AcurosPT 13.7.20. Anterior pencil beam scanning beams of 197, 200, and 210 MeV were used to penetrate the pelvis of a male Alderson Radiation Therapy Phantom. Two-dimensional ionization chamber array MatriXX PT was positioned directly under the treatment couch to detect exit dose. Measurements were compared to three-dimensional dose cubes calculated with MCDC from both TPS using site-specific gamma criteria.

Results: Based on the best three-dimensional match of dose distributions, range disagreements for the anterior-posterior travel through the pelvis torso of ~20 cm water equivalent thickness were within 4 mm between TPS and measurements. However, there was a potential underestimate of the proton range up to 4 mm when sacral bones were dominant, i.e., ~2% level for this anthropomorphic phantom. For the 210 MeV beam in uniform regions, AcurosPT's calculated dose was ~2% lower than that of RayStation's. To achieve 90% pass rate, gamma criteria range from 2 mm/2% in brain to 4 mm/4% in lung and 5 mm/5% in pelvis.

Conclusion: Pseudo proton radiography beam measurements are a feasible technique to determine site-specific MCDC accuracy in heterogeneous media.

PTC58-0270

FRoG: A platform for rapid and robust clinical dose calculations in hadron therapy

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Radiotherapy with protons and heavier ions landmarks a novel era in the field of high-precision cancer therapy. To identify patients most benefiting from this technologically demanding therapy, fast assessment of comparative treatment plans utilizing different ion species is urgently needed. Moreover, to overcome uncertainties of actual *in-vivo* physical dose distribution and biological effects elicited by different radiation qualities, development of a reliable high-throughput algorithm is required. To this end, we engineered a unique graphics processing unit (GPU) based software architecture allowing rapid and robust dose calculation. Fast dose Recalculation on GPU, FRoG, currently operates with four particle beams, i.e., raster-scanning proton, helium, carbon and oxygen ions. Designed to perform fast and accurate calculations for both physical and biophysical quantities, FRoG operates an advanced analytical pencil beam algorithm using parallelized procedures on a GPU. Clinicians and medical physicists can assess both dose and dose-averaged LET distributions for proton therapy (and eventually D_{RBE} by applying variable RBE schemes) to further scrutinize plans for acceptance or potential re-planning purposes within minutes. In addition, various biological model predictions are readily accessible for heavy ion therapy, such as LEM and MKM. FRoG has been extensively benchmarked against gold standard Monte Carlo simulations and experimental data. Evaluating against commercial treatment planning systems demonstrates the strength of FRoG in better predicting dose distributions in complex clinical settings. A summary of the recent clinical investigations with FRoG will be presented.

PTC58-0274

Raster-scanning helium ion beam therapy: development and validation of a novel treatment planning system for biophysical modeling and optimization

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Since 2009, over 5000 patients have been treated with proton (^{1}H) and carbon (^{12}C) ion beams at the Heidelberg Ion Therapy Center (HIT). By 2020, HIT will begin the first clinical raster-scanning particle therapy program using helium (^{4}He) ions, which exhibit favorable biophysical properties intermediate of clinically used light and heavy ions. Today, a commercial treatment planning system (TPS) for ^{4}He ions does not exist. This calls for an extensive development, testing and verification of a TPS for ^{4}He ions, exploring both physical and biological dose models.

This year, a GPU-based dose computation code for particle therapy (FRoG) was developed at HIT. Due to its parallelized computation scheme, sophisticated beam model and outstanding performance in conditions with anatomical complexity, FRoG performs forward dose calculations within minutes (in contrast to full simulation with hour-long runtimes) in excellent agreement with the clinical gold standard Monte Carlo simulations and measurements. Recent efforts focus on dose optimization (both physical and biological) for raster-scanning ^{4}He ions beam therapy. A fully functional TPS within the FRoG framework will be devised and clinically integrated for ^{4}He ion beams.

Furthermore, biological phenomena of ^{4}He ion beams remains poorly explored since the shutdown of clinical trials at the Lawrence Berkeley Laboratory (LBL) in the early 1990's. Potential biophysical and mechanistic approaches to modeling the relative biological effectives (RBE) in the clinic are under investigation in preparations for the first in-man treatment with raster-scanning ^{4}He ion beams.

PTC58-0168

Characterisation of the secondary neutron production with the MONDO project: an innovative tracker of ultra-fast neutrons optimised for PT applications

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The secondary fragments produced in Particle Therapy (PT) are responsible of an additional dose generally negligible with respect to the treatment one. However, secondary neutrons can travel a long path inside the patient and release energy in- and out-of-field. Such additional dose is organ and position dependent. This unwanted contribution increases the risk of developing secondary cancers: Late insurgences are particularly crucial in paediatric patients (recidive strongly impacts the life expectation and quality). A complete secondary neutron spectra (energy and angular distributions) characterisation is eagerly needed to optimise the treatment planning and is still missing. Moreover, no existing detector is able to efficiently separate the secondary neutrons from the ternary neutral component generated in the iterative interactions of fragmentation products with the treatment room (walls, nozzle etc. . .) and the patient itself. MONDO is a tracker optimised for the ultrafast neutron detection exploiting single and double elastic scattering interactions. The detector is a matrix of thin plastic scintillating fibres ($\sim$250μm), assembled in x-y oriented layers (total size 15x15x15cm3). The tracking of both recoil protons allows for a complete neutron four-momentum reconstruction. An innovative SPAD based system with integrated electronics has been designed for the fibres readout (SBAM sensor). The detector performance has been studied with a MC FLUKA study. An energy resolution of $\sim$10% is expected for neutrons in the ultrafast energy range while the expected back-pointing resolution is $<$ 1 cm (neutron source @20 cm). The MONDO expected performance and the readout chip calibration results will be presented.

PTC58-0118

NanOx (NANnodosimetry and OXidative stress) a novel model to predict RBE for hadrontherapy

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Optimization of treatment by hadrontherapy still relies on a good RBE estimation. The development of biophysics models is expected to improve the accuracy of its estimations and offers many perspectives of treatment personalization based for instance on imaging or biomarkers. In this context, we created and developed the novel model NanOx, [1], through a rigorous framework. Cell killing is induced by the generation of local events, defined at nanoscale, and nonlocal events. It is calculated from the simulation of tracks by Monte Carlo through the estimation of 2 new quantities: the restricted and the chemical specific energies. Taking into account the stochastic effects of physical and chemical events from nanoscale to macroscale is a computing challenge. Therefore, NanOx is built with a multiscale strategy.

We have already applied NanOx model for 3 different cell lines and obtained a good agreement with experiment data, competitive with the other models. In particular, NanOx reproduces the shoulder at high LET and the overkilling effect. We also show that the NanOx parameters can be determined from only the experimental determination of cell nucleus radius, cell survival to X-rays and the RBE value for one intermediate- and one high- LET ion beams [2].

The presentation of the NanOx basics will be follow by the results and the preliminary estimation of cell survival at different positions of SOBP undertaken in the context of recent experiments. [1] Cunha M. et al. PMB-2017, 62(4), pp.1248-1268. [2] Monini C. et al. Cancers-2018 Mar 21;10(4). pii: E87.

PTC58-0711

Investigating the best mass density value for adipose tissue

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When looking at a frequency distribution of the number of voxels vs Hounsfield unit for most anatomical regions, significant peaks are observed in the adipose (HU=-100+15) and soft tissue (HU = 50+10) regions suppressing any peaks in the bone region. This means that using the correct relative stopping powers (RSP), obtained from the mass density ($\mathbf{r_m}$), in the soft tissue and adipose regions are crucial for accurate proton range calculations. Measuring the HU for tissue substitute materials to obtain the input data for the Stoichiometric method proposed by Schneider et al, allows for only one measured data point in the Adipose region. Our CT scanner measures a HU of -45 + 8 for the Adipose sample which is higher than the typical HU observed for adipose in real patients. Plotting the $\mathbf{r_m}$ for Adipose (0.95 recommended by RayStation) against the HU measured for the Adipose sample renders $\mathbf{r_m}$ values < 0.95 for adipose in the patient's body. We constructed a phantom using real lamb fat and calculated a proton beam traversing the fat phantom. We measured the dose beyond the fat phantom and compared the measured dose with dose distributions calculated using HU to $\mathbf{r_m}$ curves that differ in the Adipose region. The measurements revealed that using the HU to $\mathbf{r_m}$ curve obtained using the stoichiometric method yielded the best agreement between measured and calculated dose distributions.

PTC58-0551

Effect of CT number-to-stopping power ratio conversion models on proton dose calculation in tissues

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The goal of radiotherapy is providing tumor cells with high dose at a low complication rate of normal tissues. Protons are light ions that have the Bragg peak characteristic in the depth dose distribution that is optimal for minimizing dose to surrounding normal tissues. In proton therapy treatment planning, computed tomography (CT) images are usually required for target delineation and dose calculation. The CT number is converted to proton stopping power ratios (SPR) of medium to water. The conversion is used to find water equivalent pathlengths (WEPL) of tissue voxels, which are sequentially applied to select the initial proton energy. Recently, a MATLAB-based proton therapy treatment planning system called PSPLAN based on the pencil beam scanning technique and pencil beam algorithm has been developed. PSPLAN requires CT images and calculates proton SPR based on tissue compositions and elemental mass stopping power extracted from the PSTAR database. The previous study has shown Bragg peak displacement in tissue in the range of 2-5 mm between PSPLAN and Monte Carlo simulation. In this work, we will compare SPR calculated by the different databases and investigate the effect of CT number-to-SPR conversion models on 3D dose calculation in tissues. The calculation is carried out on PSPLAN and uses PHITS Monte Carlo simulation as the golden standard. Comparison of proton dose distributions and ranges will be presented. Moreover, the effect of energy dependence of CT number-to-SPR conversion models will be discussed.

PTC58-0725

Radiobiological impact of pencil beam and Monte Carlo algorithms on IMPT breast plans

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Purpose: RayStation TPS employs pencil beam (PB) and Monte Carlo (MC) algorithms for proton dose calculations. The purpose of this study is to evaluate the radiobiological impact of PB and MC on the intensity modulated proton therapy (IMPT) breast plans.

Methods: The current study included 13 patients, and each patient was treated with 1–2 proton beams to the whole breast/chestwall (CW) and regional lymph nodes in 28 fractions for a total dose of 50.4 Gy(RBE). Total clinical target volume (CTV_Total) was generated by combining individual CTVs: AxI, AxII, AxIII, CW, IMN, and SCV. All beams in the study were treated with a range shifter (7.5 cm WET). For each patient, three sets of plans were generated:(i)PB optimization followed by PB dose calculation (PB-PB),(ii)PB optimization followed by MC dose calculation (PB-MC), and (iii)MC optimization followed by MC dose calculation (MC-MC). For a given patient, each plan was robustly optimized on the CTVs with same parameters and objectives. The Possion LQ model was used to calculate tumor control probability (TCP). The Mann–Whitney U-test was used to determine the statistical significance ($P<0.05$).

Results: In comparison to PB-PB plans, PB-MC plans showed reduction in TCP by average of 2.1%($P<2\times10^{-4}$) for AxI,1.5%($P<4\times10^{-4}$) for AxII,1.8%($P<2\times10^{-4}$) for AxIII,1.8%($P<15\times10^{-4}$) for CW,2.7%($P<4\times10^{-4}$) for IMC,2.8%($P<1\times10^{-4}$) for SCV,1.8%($P<2\times10^{-4}$) for CTV_Total. In contrast, MC-MC plans achieved TCP similar to PB-PB plans ($P>0.05$).

Conclusion: If MC is more accurate than PB as shown in the literature, PB slightly overestimated the TCP in our study. Further work on proton MC is warranted for IMPT breast treatments.

PTC58-0281

Induced radioactivity as an echo of particle therapy

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Particle therapy is the most promising form of radiation therapy of tumors, but there still remain unresolved puzzles indicating that our understanding of the complexity of hadron therapy is not complete. The aim of this work is to measure radioactivity induced in the human body during tumor treatments with using particle beams and assessment of its influence on therapy effects and causation of secondary tumors.

In order to find the sources of induced radioactivity in the patient's body, the targets (materials similar to human tissues like pig liver) were irradiated with beams commonly used in hadron therapy (60 MeV protons and nuclear reactor neutrons). After irradiation, the samples were measured using the low-background spectrometer. Based on Geant4, the Monte Carlo simulations were simultaneously performed to estimate the dose from induced radioactivity.

The results of our experiments suggest that additional dose is rather low. For bigger tumors and beams of higher energies, the contribution of induced radioactivity in total dose could be higher. Moreover, as we can see in the case of Proton Boron Cancer Therapy, even a small amount of specific element (in the case of PBCT - B-10) can significantly change the therapeutic effects. So the effect of induced radioactivity cannot be omitted and has to be estimated and taken into consideration during treatment planning.

PTC58-0331

Optimizing spot and trimmer positioning for a dynamic collimation system

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Aim: The Dynamic Collimation System (DCS) is an experimental technology that is capable of providing energy layer-specific collimation during pencil beam scanning (PBS) proton therapy. Recent studies suggest that a substantial amount of healthy tissue sparing and increase in target conformity can be achieved when utilizing PBS with a DCS. These results warrant further investigation into whether additional improvement can be obtained by developing optimization techniques unique to the DCS.

Methods: A treatment planning optimizer was designed and integrated into a research-based treatment planning system. Direct parameter optimization (DPO) was used to determine both spot and trimmer positions with gradient descent techniques on a set of three treatment plans, each consisting of two treatment fields. The DPO method was also compared directly against the trimmer selection algorithm (TSA) initially used in the DCS treatment planning studies of Smith and Moignier.

Results: A comparison of the dose-volume histograms among the three treatment plans indicate that the DPO method improved the target conformity over the TSA technique while maintaining an equivalent target coverage. The increase in computational resources is minimal, especially since the proposed DPO technique can be parallelized across multiple CPUs.

Conclusion: Both the TSA and DPO techniques can achieve superior target conformity and healthy tissue sparing in comparison to other contemporary PBS treatment modalities. While the improvement of DPO over TSA is small, it is still important should any compromises to the plan conformity be necessary to lower the expected treatment time or increase plan robustness.

PTC58-0428

Integration and application of an independent GPU-based dose engine (FRoG) at the Normandy Proton Therapy Center

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Following the installation and commissioning of the Proteus®ONE solution by IBAin conjunction with the RayStation® (RaySearch, Stockholm, Sweden) treatment planning system (TPS), the CYCLHAD Center in cooperation with Center François Baclesse (CFB) began administering proton therapy treatments in July 2018.

Contrary to conventional radiotherapy, there is no widely accepted practice for verification of clinical performance using independent dose calculation software in proton therapy. Monte Carlo codes developed and maintained in-house offer gold-standard accuracy but require substantial physics and programming expertise for time- and hardware-intensive computation. Moreover, despite evidence of variable relative biological effectiveness (RBE) for protons, there is no streamlined solution to access innovative biophysical dose computation (e.g. next-generation beam models, dose-averaged linear energy transfer (LET_d) and variable RBE models). These current setbacks in the field impact clinics which lack large research support teams dedicated to clinical physics.

The FRoG platform (Fast dose Recalculation on GPU) approaches these shortcomings by providing a GPU-accelerated analytical dose engine, capable of effective dose computation within minutes. With FRoG as an auxiliary system for advanced dose computation and verification, physicians and physicists can better predict the ‘‘delivered biological dose’’ to the patient in challenging clinical cases, as well as incorporate LET_d into treatment planning and clinical decision-making. Here, we present a detailed account of FRoG’s commissioning at CFB in preparation for advanced treatment planning studies as well as a dosimetric evaluation of the clinical TPS against FRoG and measurements using advanced anthropomorphic phantom set-ups (CIRS Proton Therapy Dosimetry Head, Model 731-HN).

PTC58-0455

Optimization techniques and systematic robustness evaluation in proton therapy

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At the Normandy Particle Therapy Center, patient treatments began in July 2018 using the ProteusOne (IBA). Treatment optimization for brain cases have been performed using SFO-IMPT with robust optimization on CTV with 3%/3mm uncertainties to the stopping power conversion and patient position, respectively, and calculated via a Monte Carlo dose engine within the RayStation treatment planning system (RaySearch). Prior to the planning of new localization such as head and neck or pelvic tumors, and the introduction of MFO-IMPT, a campaign to compare the various delivery techniques, MFO/SFO- IMPT delivery, with planning on PTV or robust on CTV is underway. For the different localization, the techniques are investigated and compared through a robust evaluation and the time needed to achieve the plans. While robust optimizations appear superior in most of the cases with MFO-IMPT, they can be equivalent to those achieved on PTV for SFO-IMPT but with a time cost in the favor of PTV optimization. This could be of particularly importance for the pelvic region where target size and uncertainties are larger than in brain cases.

Concurrently, systematic robust evaluations were performed for all cases treated so far at the proton center with SFO-IMPT to validate the planning with clinicians. Among the 100 cases simulated (figure1) for uncertainties within the planning boundary, the numbers of cases meeting and failing the dose/volume constraints are evaluated for further clinical discussion and adaptation of the plan if necessary.

Robust optimization shows promise in fully exploiting the benefits of proton-therapy with an optimal treatment quality.

PTC58-0640

Proton simulation in the Monte Carlo code PENELOPE

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Purpose and Objective: PENH is a module for Monte Carlo (MC) simulation of protons in the PENELOPE code. In contrast to the earlier PENH-S by Sterpin et al. [1], PENH is not limited to the materials implemented in the hadronic interaction model and can be extended based on the ENDF-6 database [2]. The purpose of this work is to benchmark this module.

Material and Methods: PENH results are compared with experimental data and simulations done with TOPAS MC v3.1p2 [3], RayStation 6 MC [4] and PENH-S. For all simulations a measurement-based Fermi-Eyges beam model was used, whereby the source can be described as a linear quadratic function [5]. A nominal energy of 225 MeV was used.

Results and Discussion: The depth dose profiles taken at varying radii are shown in the figure. All codes agree with experimental data for radii up to 3 cm. Results from TOPAS coincide with experimental data up to six orders of magnitude below the maximum. Results from both RayStation and PENH qualitatively reproduce the experimental behavior for radii between 3 and 6 cm. Results from PENH-S qualitatively reproduces the central beam axis.

Conclusion: The differences between TOPAS and PENH arise from the different physics models and tracking schemes. We conclude that the physics modeling of the PENELOPE/PENH code yields results consistent with measurements at relevant dose levels for treatment planning.

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PTC58-0400

Dual-energy CT-based accurate relative stopping power mapping using 3D generative adversarial networks

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Purpose: The accuracy of dual-energy CT (DECT)-derived parametric maps is directly affected by the level of photon noise and image artifacts. Such inconsistency degrades the accuracy of the physics-based mapping technique and affects subsequent processing for clinical applications. In this study, we propose a deep-learning-based method to accurately generate a relative stopping power map (RSPM) as an alternative to physics-based dual-energy approaches.

Methods: We manually segmented head-and-neck DECT images into brain, bone, fat, soft-tissue, lung and air, and then assigned different RSP values into the corresponding tissue types to generate a reference RSPM, which is the training target of our deep-learning model. We proposed to integrate a residual block concept into a cycle-consistent generative adversarial network framework to learn the nonlinear mapping between DECT and reference RSPM. This learning-based RSPM generation method was tested with 18 head-and-neck cancer patients. Mean absolute error (MAE) and mean error (ME) were used to quantify the differences between the generated and reference RSPM.

Results: The average MAE between generated and reference RSPM was 0.031 ± 0.004 and the average ME was 0.015 ± 0.005 for all patients. Comparing to the physics-based method, the proposed method could improve RSPM accuracy and had comparable computational efficiency after training.

Conclusion: We have developed a novel learning-based method to effectively capture the relationship between DECT data of tissue substitutes and reference RSPM, subsequently used it to generate accurate RSPM, and demonstrated its reliability. The proposed deep-learning-based approach has the potential advantages of producing unbiased and robust RSPM for proton dose calculation.

PTC58-0006

Clinical outcomes and toxicity comparison of treatment with Gamma Knife and proton therapy for uveal melanoma

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The patients treated with Gamma Knife (GK), or Proton therapy (PT) for uveal melanoma were reviewed. We analyzed post-operative visual outcomes and toxicity if visual outcomes varied with proximity to the optic nerve or fovea. The two patients with choroidal melanoma were still alive with no evidence of tumor progression or distant metastasis. In case 1 patient, the fundoscopic after GK showed hyperpigmentation of tumor surface, distinct borderline of tumor margin, and tumor shrinkage. Significant tumor thickness reduction was observed in one of the choroidal melanoma patients and the metastasis patient. In case 2 and 3 patients, post-treatment ultrasonography after GK showed serous retinal detachment disappearance. In one melanoma patient, post-gamma knife 3 months, patient complained about blurred vision of right eye. According to the references were compared the visual outcome, patients treated with PT retain better vision post-operatively however possible confounding factors in study include age, tumor location and systemic morbidities. Sikuade *et al*. report treatments achieved excellent local control rates with eye retention in 98% of the GK group and 95% in the PT group. The GK group showed a poorer visual prognosis with losing acuity compared to with PT. A report from Verma *et al*. showed PT could reduce ocular toxicities in patients with uveal melanoma. Five-year local control rates exceed 90% overall survivals range from 70–85% using proton beam radiotherapy. Only 7–10% of uveal melanoma patients needed eye removal after treatment.

PTC58-0250

Development of Monte Carlo-based port simulation tool for carbon-ion therapy using broad beam method

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Aim: At Gunma University, dose distributions calculated by a treatment planning system (TPS) are verified by measuring the absorbed dose distributions for carbon-ion therapy. However, this method requires a significant amount of beam time, and it provides no information about the biological effects. To address these issues, we aim to introduce a Monte Carlo simulation system, PTSIM, based on Geant4, as an alternative verification tool.

Methods: In this study, first, we evaluate the influence of the differences between two nuclear interaction models—the binary cascade model and the quantum molecular dynamics model of Geant4 on dose distributions—and the values of the relative biological effectiveness. Then, we modify the PTSIM to simulate a layer-stacking irradiation method and verify its simulation results by comparison with calculations by a TPS and measurements.

Results: The preliminary result of the comparisons between the simulation of each nuclear interaction model and the measured dose distributions showed a difference of 3% in the region shallower than the maximum depth of the carbon-ion beam range. A function to simulate the layer-stacking irradiation method has been implemented to the PTSIM. The simulation function is being verified.

Conclusions: The simulations of the two nuclear reaction models were evaluated by comparison with the measurements. A function to simulate the layer-stacking irradiation method was implemented to the PTSIM.

PTC58-0119

Dosimetric impact of the low dose envelope on dose distributions associated with different carbon-ion pencil beam models

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Purpose: Deficient description about the low dose envelope of a carbon-ion pencil beam in treatment planning system (TPS) would result in deviations in dose calculation. This work investigates the dosimetric effect of the low dose envelope and makes evaluation about the calculation accuracy of different pencil beam models using different virtual spherical target volumes in water tank.

Material and Methods: Based on Monte Carlo (MC) simulation and dose optimization-oriented iterative least square method, comparisons of the dose distributions between the MC simulations and calculations using the single, double and triple Gaussian models and our newly-proposed one, double Gaussian-logistic model, were conducted for both virtual homocentric spherical target volumes in diameters of 3 cm, 5 cm and 8 cm at the penetration depth of 150.5 mm, and the same-sized spherical target volumes in diameter of 3 cm located at the depths of 114.5 mm, 150.5 mm and 186.5 mm in water.

Results: The dosimetric effect of the low dose envelope increased in depth along the beam incidence direction for the same-sized spherical target volumes in the water tank, while it was irregular for the concentric spherical target volumes with the various diameters. The superiority of the double Gaussian-logistic model over the others was demonstrated further and manifested most obviously in small target volumes, especially at deeper depths.

Conclusion: The low dose envelope of carbon-ion pencil beam should be fully considered in accurate dose calculation. The double Gaussian-logistic model has been demonstrated to be a good option.

PTC58-0484

The role of robust optimization on brain proton therapy using MRI-based synthetic CT

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Purpose: To investigate the dosimetric accuracy of synthetic CT (sCT) based proton dose distributions in brain patients and the role of robust optimization in compensating for any existing uncertainties in the HU of sCT.

Methods: sCTs were generated from MRI images using our advanced deep-learning-based method. Proton plans (54Gy in 30 fractions) with and without robust optimization were created on 31 brain patients ontheir planning CT (pCT) and applied to the corresponding sCTs. Dosimetry parameters (CTV mean, D95, and V100) were calculated. Mean HU difference (MHD) between pCT and sCT were calculated in the area enclosed in the 10% isodose lines. Gamma analysis was performed in the same region for the comparison of dose distributions between sCT- and pCT-based dose distributions.

Results: Without robust optimization, CTV mean, D95, and V100 were 55.4±0.4Gy vs 55.3±0.3Gy, 54.5±0.3Gy vs 54.2±0.3Gy, 98.0% (nominal) vs 96.6%±1.9%, respectively, for pCT-based vs sCT-based dose distributions. The max reduction of D95 was 1.85% for the sCT-based plans. Nine patients (29%) had V100 reductions >2% (max 6.1%). For this subgroup, with robust optimization using 3.5% range uncertainty, the D95 and V100 reduction in sCT plans were significantly reduced, 0.93% vs 0.2% (p=0.03) and 3.8% vs 0.3% (p<0.001), respectively. The MHD for all patients was 44.4±36.2 HU. Gamma analysis using 2%/2 mm at 10% dose threshold for all plans without robust optimization showed > 99.5% pass rate.

Conclusion: The use of robust optimization improves target coverage for sCT based proton plans. MRI-based simulation and proton therapy treatment planning using sCT is feasible for brain tumor patients.

Physics: Dose Calculation and Optimisation Poster Discussion Sessions

PTC58-0217

A Monte Carlo-based 4D-dose calculator and robust optimizer for a pencil-beam scanning proton-therapy system

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Purpose: To assist 4D treatment planning for spot-scanned-delivered protons in the presence of respiration by developing Monte-Carlo based 4D packages for dose calculation and robust optimization.

Methods: A GPU-based platform was created to calculate 4D dose from an input treatment plan to assess the plan's stability under patient breathing as characterized by 4DCT. The 4D calculation began with a beam-delivery simulation which divided the planned spots across the breathing phases. An in-house Monte Carlo dose engine was then used to calculate sub-doses on each of the breathing phases. The sub-doses were then summed onto the end-exhalation phase using deformable-image-registration based accumulation techniques. The beam-delivery simulation and dose-accumulation algorithms were incorporated into a robust optimization engine. The doses from potential spots were calculated and deformed to the end-exhalation phase before being accumulated as a weighted sum, with the weights dictated by beam-delivery simulations. The 4D doses were affected by beam-delivery uncertainties due to variable breathing and delivery parameters; these uncertainties were included in the optimization algorithm as robust scenarios in addition to range and setup uncertainties.

Results: The uncertainties from the beam-delivery simulation led to moderate variations in the calculated 4D dose-volume histograms as seen in Figure 1. The optimizer converges, as in Figure 2, even with updating the phase weighting periodically to account for updated spot weights.

Conclusions: A 4D dose calculator and robust optimizer were developed to create and assess 4D treatment plans. based on Monte-Carlo calculated dose, realistic simulations of the proton delivery, and deformable-image-registration based dose accumulation.

PTC58-0330

Optimized proton pencil beam scanning source in Monte Carlo dose calculation for small-collimated fields

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Introduction: A proton pencil beam scanning (PBS) source with optimized spot sizes and divergences at field-dependent phase-space plane was demonstrated in the Monte Carlo (MC) dose calculation for small-collimated PBS fields.

Methods: The proton PBS phase-space file of spot sizes and divergences using two virtual source-to-axis distances at the position above the aperture were constructed from an extrapolated source database to have the best mapping with the commissioning spot shapes measured at the isocentric plane, and upstream/downstream by 15 cm (Figure 1). The optimized PBS source was then used in Geant4 MC code for small-collimated PBS fields. The results were compared with the calculations using a published PBS MC model (Florini et al., Med. Phys. 2018), the commercial MC treatment planning system (TPS, RayStation 6 SP1.1 Clinical, Monte Carlo v4.0), and the measurements.

Results: The planar and depth doses calculated using both optimized and published PBS source were comparable with MC TPS calculations. The uses of optimized and published PBS source models showed >98% Gamma passing rate (DD: 3%, DTA: 3mm) in the planar doses compared with the MC TPS calculations for a 10×10-cm^2 PBS field trimmed by a 4×8-cm^2 half-blocked aperture. Improvement of agreement was found in the integral depth-dose measurements (2.5-cm diameter multi-layer ionization chamber array) for the 10×10-cm^2 PBS field collimated by a 2-cm diameter aperture as shown in Figure 2.

Conclusions: The optimized proton PBS source term could be used in the independent dose check for small-collimated PBS fields potentially for the proton stereotactic radiosurgery.

PTC58-0606

Optimization of intensity modulated proton therapy using track-ends and variable relative biological effectiveness

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Purpose: Compare the RBE-weighted dose (RWD) for intensity modulated proton plans (IMPT) optimized using a constant relative biological effectiveness (RBE), track-end objectives and a RBE model for DNA double strand break (DSB) induction.

Methods: IMPT plans (RWD of 54 Gy in 30 fractions) for three intracranial patients were optimized using a (1) constant RBE=1.1 (DOSEopt), (2) RBE=1.1 with track-end penalization in organs at risk (OARs) (TEopt), and (3) the RBE model for DSB induction (RWDopt). The same clinical objectives, expressed as the RWD, were used for all plan optimizations. Plan quality is evaluated in terms of the RWD for OARs, isodose contours, and dose-volume histograms (DVHs). The dose-averaged linear energy transfer (LET_d) is also reported.

Results: All plans met the clinical RWD goals for the OARs with RBE=1.1 and the RBE model for DSB induction. When an alternate RBE model (Wedenberg model for cell survival) is used for plan quality evaluation, plans optimized using the DOSEopt and RWDopt methods did not meet the clinical criteria for some OARs. Plans optimized with TEopt method satisfied the clinical goals for all relevant OAR. For intracranial patients, plans optimized using the TEopt and the RWDopt methods increase target LET_d and RWD, resulting in slightly better CTV coverage than the DOSEopt plans and a constant RBE of 1.1.

Conclusion: IMPT plans optimized using the RBE for DSB induction (RWDopt) or track-end penalization methods (TEopt) may be effective at reducing OAR treatment toxicity without the need for tissue-specific biological parameters.

PTC58-0668

Systematic error in discrete time sampling of 4D-Monte Carlo simulations for particle therapy

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In 4D-Monte Carlo simulations, time can be sampled in a sequential or random mode by sampling discrete or continuous functions. In sequential mode, time is sampled using a fixed number of sequential time steps that need not be evenly spaced. In random mode, time is continuously sampled. The sequential mode is conceptually more intuitive and straightforward to implement. However, systematic errors may result should critical time bins be under-sampled such as may occur when using a reduced number of particle histories. This does not occur in random mode.

In this work, a well characterized proton beam line using rotating propeller (100 ms/rotation) to generate a SOBP for eye treatments was simulated in random and sequential mode using the TOPAS Monte Carlo tool. Dosimetric comparisons were made between the random and sequential mode with three different time steps: 1 ms, 2 ms, and 5 ms. The systematic error introduced by sequential mode by under-sampling uniformly spaced time bins was determined. The same source fluence was used in all simulations to maintain the same precision in the calculated dose distributions.

Systematic errors in absolute dose distributions, introduced by the sequential mode, increased as the time step increased, reaching 4% for the largest time step considered (figure 1).

The use of sequential mode in 4D Monte Carlo simulations requires ensuring that the choices of time step size, number of time bins, etc. does not result in clinically significant systematic errors. Comparison to simulations done using the random mode is useful for this purpose.

Physics: Image Guidance

PTC58-0418

Experimental validation of Monte Carlo simulations for single detector proton radiography with scanning beams

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Purpose: To compare the simulation results of energy-resolved dosimetry (ERD) technique for proton radiography applications with experimental data and to estimate the achievable accuracy in this technique.

Methods: A solid water wedge (35 cm x 35 cm) is kept in the path of a scanned pencil beam of protons and a 2D detector is used to measure dose at the exit. The energy of the beam is increased from 100 MeV to 225 MeV in steps of 3 MeV to measure the dose which is stored as ERDF library. The setup is also simulated in GATE to retrieve the ERD functions (ERDFs). The detector thickness and energy spread are then optimized to match with the experimental results. These ERDF maps are used to generate the WEPL map for water stairs geometry and inserts configuration.

Results: The WEPL map for stairs and inserts are generated by comparing the pixel-wise ERDFs with the simulated and experimental ERDFs. WEPL values calculated from both the ERDFs yield almost similar results with a maximum error of about 4%.

Conclusions: From the results, we conclude that the ERD functions obtained from simulation are a potential alternative to experimentally obtained ERDFs which can drastically reduce the time involved in obtaining the experimental ERDFs.

PTC58-0608

Deep learning technique for generating the WEPL images in proton radiography

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Purpose: To apply deep learning techniques for prediction of WEPLs in proton imaging using energy-resolved dose functions (ERDF)

Method: The simulation set up consists of a solid water wedge (35 cm x 35 cm) in the path of the scanned proton beams and a water box (30 cm x 30 cm x 0.1 cm) with voxel ($600 \times 600 \times 1$) is kept after the wedge to measure the dose is created using GATE simulation toolkit. The beam energy is increased from 100 to 250 MeV in steps of 3 MeV and the ERDF library is generated for different WEPLs. This database is used for training a deep-learning model which is then used for predicting the WEPL of a water phantom with staircase geometry.

Results: The first results show that though the WEPL values differ from the true values, the processing time taken for this algorithm is far less compared to the conventional chi-squared minimization.

Conclusions: Deep learning techniques offer a new avenue of analysis in the field of proton imaging especially in reducing the computation time. The technique needs to be fine-tuned with respect to the model parameters and features in order to predict the WEPLs within clinically acceptable limits.

PTC58-0611

Quality of radiographs versus the imaging dose from single detector using ERDF method

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Purpose: To study the variation of the accuracy of the WEPL with the number of layers in proton radiography using energy-resolved dose functions (ERDF).

Method: The ERDF is calculated using a set up that consists of a solid water wedge (35 cm X 35 cm) and a 2D detector (Lynx, 900 cm^2 active area and 0.5mm resolution) to measure the dose. An imaging field consisting of a set of PBS layers (100 MeV to 250 MeV in steps of 3 MeV) is used to deliver a uniform dose. The water wedge is then replaced by head phantom and WEPL values are estimated from ERDFs using minimum chi-square method. The number of layers is now decreased and the variation and the accuracy of the WEPL in each of these cases are calculated.

Results: The estimated WEPL by selecting 24 PBS layers and 16 PBS layers have an error of 2% and 5% with the total dose reduced by a factor of 2 and 3 respectively. Further reduction in the number of PBS layers increases the error to above 7%.

Conclusions: We have studied the quality of the WEPL images and their dependence on the number of PBS layers used. The results help in understanding the optimal number of layers for achieving clinically acceptable dose and also indicate that there is scope for progress to improve the WEPL accuracy, for example using machine learning techniques.

PTC58-0712

A method for estimating the effect of density changes on particle range using water equivalent path length

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Introduction: The precision of particle therapy is sensitive to changes in density in the particle path. The difference in the water equivalent pathlength (WEPL), from planning CT (pCT) to the anatomy of the day, allows for an estimation of the effect of density changes on particle range. However, ΔWEPL assumes the point of calculation origin is anatomically the same on both CT modalities. This study therefore aims to provide a method for estimating the effect of density changes to the dose distribution, without the need for a full dose recalculation.

Method: The method used two images modalities, the pCT and a CT-like image of the day (dCT), which were both translated to stopping power values. The iso-dose of a given beam was extracted from the plan as physical points ($P_{iso\text{-}dose}$) in pCT space (P_{pCT}). We assumed that the pCT field configuration had the same physical positions in dCT space. From each point in $P_{iso\text{-}dose}$ the WEPL was calculated as the sum of linearly interpolated values ($S_{pCT}(\boldsymbol{p})$), at each step along the opposite beam direction ($\boldsymbol{b}$), until the edge of the image. Taking the same $P_{iso\text{-}dose}$ from the pCT and calculated the intersection, $\boldsymbol{p}_{edge}$, in the direction of $\boldsymbol{b}$, with the nearest bounding plane of dCT. Accumulated from $\boldsymbol{p}_{edge}$ stepping in the $-\boldsymbol{b}$ direction until $WEPL_{pCT}$ was reached, and thus $\boldsymbol{p}_{final}$, satisfying.

Conclusion: Our method produces a per-beam pseudo-iso-dose on the dCT, which will be an estimate of the per-beam iso-dose if recalculated on the dCT. We have implemented this method with scatter-corrected CBCTs.

PTC58-0215

Performance of 2D and CBCT imaging for patient positioning at McLaren Proton Therapy Center

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Introduction: The characteristics of proton beams allow for steep dose fall off between normal tissue and target. Evaluating the accuracy of patient positioning is important to ensure correct dose delivery. The McLaren Proton Therapy System (MPTS) is equipped with a kV-imaging system capable of orthogonal and CBCT imaging from an independent gantry.

Methods and Materials: The system was tested according to requirements outlined in TG 142 and TG 179. The CIRS Isocube device and anthropomorphic phantom were simulated with a slice thickness of 1mm. Orthogonal and CBCT imaging were planned for image registration evaluation. The accuracy was accessed by placing the phantoms at a known offset from isocenter and imaged at three couch angles 0, 180 and 270 degrees with both modalities. The imaging hardware is controlled by Ehmet dx XIS (X-ray Imaging Software) and the image registration is done with MIM Software.

Results: Deviations from expected values were below 1 mm and 1 degree. Average deviations for orthogonal imaging were 0.21, 0.03 and -0.11 mm for x, y, z and 0.17, 0.04 and 0 degrees for yaw, pitch, and roll. Average deviations for CBCT imaging were 0.31, 0.42 and 0.41 mm for x, y, z and 0.07, 0.28 and 0.18 degrees for yaw, pitch, and roll.

Conclusion: The use of both modalities with a static solid phantom yielded comparable results with repositioning after image registration and all tested couch angles within 1 mm. Future CBCT and orthogonal imaging studies with a flexible anthropomorphic phantom are needed.

PTC58-0193

Optimization of 4DCBCT image reconstruction at proton gantry systems

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Purpose/Objective: CBCT imaging has recently become available at proton therapy facilities. A 4D reconstruction of CBCT images enables daily breathing motion evaluation. In this study we compare two projection binning approaches for 4D reconstruction in terms of overall image quality and diaphragm artefacts. The aim is to establish an optimal and automatic 4DCBCT reconstruction workflow for clinical use.

Material and Methods: Two sets of CBCT-projections and Anzai signals were acquired at our proton facility for a porcine lung phantom available from the LMU, Munich. For each set, three 4DCBCT images were reconstructed applying the MA-ROOSTER method, where projection binning was performed using the (A) Anzai signal and the Amsterdam Shroud method ((B) automatically and (C) manually corrected). A visual inspection of the reconstructed 4DCBCT images was performed at the diaphragm region and the structural similarity indices (SSIM) were calculated comparing the 4DCBCT quality to 3DCBCT image quality.

Results: Figure 1 shows the coronal view of one reconstructed 4DCBCT. Increased diaphragm artefacts were observed for method (B), but the image quality improved when manually corrected (C). The best visual result is observed for method (A). Table 1 shows the structural similarity indices for the reconstructed 4DCBCT scans and projection binning methods. The best SSIM of 0.49 was achieved with method (A) for both CBCT data sets.

Conclusion: The Anzai belt signal method (A) resulted in the best image quality. As it can be performed without manual intervention, it is the preferred approach for clinical 4DCBCT reconstruction at our proton facility.

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PTC58-0031

Modelling of contributions to image variance in proton CT for application in low-dose fluence-modulated imaging

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The use of proton computed tomography (pCT) for daily in-room-imaging promises superior accuracy of relative-stopping-power images for treatment-planning and dose-recalculation according to the anatomy-of-the-day. At doses of only 1mGy, data from a prototype pCT scanner suggest improved accuracy in clinical dose calculation. Application of fluence-modulated pCT (FMpCT) may further reduce dose to healthy tissue by at least a factor of two while maintaining relative-stopping-power accuracy in the beam path [1].

To achieve prescribed non-homogeneous noise-targets with FMpCT, prior knowledge of patient-specific image variance contributions is crucial. We present a method to accurately calculate variance images from Monte Carlo simulated pCT scans. We modelled quenching effects in scintillators of the energy detector and constructed a beam model from tracking data. Variance agreement with experimental data acquired at 0.9mGy was better than ±7% for a water phantom, ±9% for a sensitometry phantom with tubular inserts (Catphan-404), and ±11% for an anthropomorphic head phantom. Subtle variance features near heterogeneities were observed (Fig.1). Furthermore, we isolated noise contributions using simulated data. While the beam energy spread added a constant variance contribution of about 20%, the component of energy straggling in the object and energy detector depends on the water-equivalent path-length. We also quantified the contribution of multiple-Coulomb-scattering and its dependency on the imaging object (Fig.2).

In conclusion, we experimentally validated the use of Monte Carlo simulations for calculating variance images with an accuracy sufficient to enable the design of FMpCT scans for daily in-room-imaging at reduced doses, and analyzed principal noise contributions. [1] Dedes et.al., Med.Phys, 45(7),2018. Acknowledgements: DFG (project #388731804,MAP).

PTC58-0046

Machine learning based detector calibration to improve the accuracy of proton computed tomography

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Proton therapy requires accurate prior knowledge of relative proton stopping power (RSP) with respect to water. Measuring RSP directly with proton computed tomography (pCT) is desirable, as it overcomes inaccuracies from converting x-ray attenuation coefficients. This work aimed at implementing a machine learning (ML) algorithm to calibrate the Phase II preclinical pCT prototype scanner [1] in order to measure RSP with sub-percent accuracy. The existing calibration method may cause ring artifacts for filtered backprojection reconstructions and sup-percent RSP accuracy is not guaranteed in ring artifacts.

In the frame of a Geant4 simulation study, we used an AdaBoost regression model (base estimators: 50 decision trees, maximum depth of 12) to predict the water-equivalent path length (WEPL) (Fig.1), which is the line integral of RSP along the proton path. Per proton, five consecutive downstream energy measurements from the five-stage calorimeter were used as input. The model was trained on pCT scans of a phantom with known WEPL and applied to an unknown cylindrical water tank. Prior to training and application, events undergoing nuclear interactions have been rejected. The ML calibration provided RSP accuracy better than 99.2% in annular region-of-interests, compared to 98.5% for the existing calibration, significantly reducing ring artifacts (Fig.2). Mean RSP accuracy was between 99.98%-99.99% in both cases.

In summary, it was possible to calibrate a pCT detector using ML methods and to outperform a current calibration in a simulation study. Our novel approach is fast to implement, highly flexible, and not limited to specific detector or phantom designs. [1] Sadrozinski,HF-W.,et al.,NIMA,831,2016,394-399. Acknowledgements: DFG (project #388731804,MAP).

PTC58-0100

OPTIma: Optimising proton therapy through imaging

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Several research groups worldwide have worked in the past years towards the introduction of a new imaging modality – proton Computed Tomography (pCT) into the Proton Beam Therapy (PBT) clinical workflow, with the aim of directly measuring a patient's tissue stopping power and reduce uncertainties in treatment margins. Among others, the PRaVDA collaboration developed the first fully solid-state imaging system for pCT and showed a reduction in relative stopping power uncertainties down to 1.6% for a number of tissue substitute materials [*Esposito et al., Phys. Med., 58, 2018*].

Building on the PRaVDA experience, a new UK-based collaboration named OPTIma was formed in 2018 to take forward the concept of a solid-state proton imaging system along the route to clinical use. The OPTIma system, currently under design, will be hosted in the Christie PBT Research Room using state-of-the-art spot-scanning delivery, providing a national facility for tissue stopping power calibration and evaluation of pCT in developing optimum and personalised treatment plans. Key aspects of the project include adapting detector technology and reconstruction algorithm to spot-scanning delivery systems, decreasing relative stopping power uncertainty to 1%, combining stopping power imaging with other aspects of the physics of proton interaction (i.e. scattering, straggling and attenuation powers) and integrating pCT with other existing imaging modalities in the clinical workflow.

An update on the status of the project, in terms of system design and simulation, as well as future use, will be presented.

PTC58-0429

Organ doses from a proton gantry-mounted CBCT system: Dependence on scanning mode

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Purpose: To evaluate the influence of different scanning modes on organ doses for a kV-CBCT system mounted on a proton therapy gantry.

Material and Methods: The proton gantry-mounted CBCT system was modelled using two different Monte Carlo codes (GATE and MCNP6). Following the validation of the two models against measurements, Monte Carlo simulations of CBCT acquisitions were performed with a full-body phantom geometry with both models. Three protocols were considered: head, thorax and pelvis. For each protocol, three scanning modes were evaluated: 360° full scan and 190° anterior & posterior scans. The resulting organ doses following the different scanning modes were evaluated and compared. To make the comparison relevant between 360° and 190° scans, the organ doses were normalized by the integral mAs of each scan.

Results: The organ doses per mAs ranged between approximately 4-20 μGy/mAs, and the highest organ dose per mAs was found with the anterior scans for 12 out of 14 organs. The trend was reversed for posteriorly located organs (*e.g.* rectum). On average, anterior scans delivered organ doses 24% higher than 360° full scans, while a 37% decrease was observed with posterior scans. For central organs such as the brain in the head protocol, the difference was minimal.

Conclusion: This study suggests that posterior CBCT scans reduce dose per mAs in the majority of organs of interest in comparison to anterior and full scans. However, the differences in image quality between the considered scanning modes should be further evaluated.

PTC58-0473

gPET: An efficient and accurate simulation tool for PET via GPU-based Monte Carlo

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Positron emission tomography (PET) is of emerging importance in advanced online-dose-verification in particle therapy with Monte Carlo (MC) method, a long-time-proved essential and accurate simulation toolkit in the refinement of PET systems. To overcome the suffering of expensive time consuming in the existing CPU-based MC toolkits for PET, we present here a GPU-based accurate and efficient MC package, gPET, dedicated for PET simulation. gPET was built on the Nvidia CUDA platform, starting with positron emission nuclei distribution in the voxelized phantom and ending with coincidence events in parameterized PET detector, with allowance of various intermediate data outputs according to user preference.

Various cases were simulated to comprehensively evaluate the efficiency and accuracy of gPET. It was found that the simulation time was 780 folds reduced with parallelization, that was 0.6s/million-history for gPET on one Nvida Titan Xp GPU (1.58GHz) card compared with 470s/million-history for GATE8.0 on one Intel i7-6850K CPU (3.6GHz) card, respectively. Meanwhile, the accuracy of gPET kept a good consistence with GATE8.0 regarding to the energy and spatial distributions of hits, singles and coincidences. For a representative simulation case of an eight-panel small animal PET with 10 million histories, the differences of energy, panel, module and crystal distributions of hits are 2.44%, 2.26%, 2.26% and 2.27%, respectively. Those for singles and coincidences are 1.26%, 0.51%, 0.51%, 1.12% and 2.91%, 2.7%, 2.7%, 2,9%, respectively. For the reconstructed images, the difference of 11 points was below 2.0%. gPET version 1.0 is available at https://github.com/UTAChiLab/gPET.git.

PTC58-0631

Monte Carlo simulations of a single volume neutron scatter camera for in-vivo range verification in proton therapy

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Introduction: Uncertainties in the beam range and Bragg peak position during treatment inhibit exploiting the full potential of proton therapy. As a unique solution to in-vivo range monitoring in proton therapy, we propose a single volume neutron scatter camera (SVSC) for detection and imaging of secondary neutrons produced in nuclear interactions.

Materials and Methods: Determination of neutron incidence angles and energies relies on two consecutive neutron elastic scatter events on hydrogen-1 in the sensitive volume of the SVSC. We investigate the expected response of the SVSC in terms of its efficiency, detected neutron profiles, and the relation between estimated "range landmarks" and the proton range using Geant4 simulations. We direct monoenergetic proton beams at 100, 160, 200 and 230 MeV onto a water phantom whereas the SVSC is modelled as a $10 \times 10 \times 20$ cm^3 EJ-309 liquid scintillator placed at 30° with respect to the direction of the incoming proton beam.

Results: The detected neutron profiles show a distinct peak and a fall-off towards the Bragg-peak location (Fig. 1A). The inflection point positions are linearly correlated with the proton beam range (Fig. 1B). Sub-mm accuracy in the estimation of inflection point positions are obtained at all energies at proton intensities as low as 1.2×10^8.

Conclusion: The proposed SVSC concept holds the potential to offer a uniquely novel solution to in-vivo range verification in proton therapy and warrant further investigations.

PTC58-0526

Feasibility of ultrahigh dose escalations of MRI-defined intraprostatic lesions with proton therapy

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Introduction: Compared to uniform prostate irradiation, delivering dose escalations to the intraprostatic lesions (IL) could provide superior outcomes for high-risk prostate cancer. This study aims to quantify the dosimetrically feasible degree of dose escalation to the MRI-defined ILs with proton therapy.

Methods: Six patients with focal ILs observed on diagnostic multiparametric MRI (mpMRI) were retrospectively selected. The ILs were manually delineated on T2W MRI and apparent diffusion coefficient maps, and transferred to the simulation CT via image registration. Proton plans were created for uniform prostate dose (70 Gy in 28 fractions), and simultaneous integrated boost to ILs with increasing escalation in 7 Gy steps. All normal tissue constraints were satisfied while escalating the dose. The increase in tumor control probability (TCP) was investigated.

Results: We found that the IL dose could be escalated to up to 140 Gy without violating the OAR constraints for anterior lesions. The TCP for ILs on average increased by 59.2% for 40% boost while the increase in normal tissue complication probability remained negligible ($<$0.3%). For lesions in the peripheral zone, rectal spacers could assist with maintaining the rectal high dose below the constraint. Photon plans for the same patients could achieve maximum IL dose escalation of up to 20% smaller than that of proton plans, depending on the location of the ILs within the prostate.

Conclusion: Ultrahigh dose escalation of MRI-defined highly malignant ILs with proton therapy is feasible and could yield significantly improved tumor control compared to conventional methods without increasing the toxicities.

PTC58-0734

R&D of neo beam ON-LINE PET system for proton irradiated volume imaging

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Proton therapy is a form of radiotherapy that enables the concentration of a dose onto a tumor by the modulation of Bragg peak. Therefore, it is very important to evaluate the proton-irradiated volume accurately. The dose-volume delivery guided proton therapy (DGPT) can be confirmed by information of positron-emitting nuclei generated in the patient body by the target nuclear fragment reaction of the incident protons on target nuclei. In this study, we designed and developed neo beam ON-LINE PET system (nBOLPs) with imaging technique in activity of generated positron-emitting nuclei for achievement of DGPT. The nBOLPs is constructed with 4 planar type detector heads with 14,400-GSO crystals of 2 mm x 2 mm x 25 mm. Performance of the nBOLPs was imaging volume of about 15 cm x 15 cm x 15 cm, detection-position resolution better than 3 mm, and detection rate better than 100 kcps. The experiment of proton beam irradiation to head & neck and pediatric phantoms was carried out for evaluation in clinical situation of proton therapy. The developed nBOLPs has great potential for high precision proton therapy with proton irradiated volume imaging and DGPT in the future.

PTC58-0195

Iterative CBCT: Improving CBCT image quality at ProBeam

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The ProBeam radiotherapy system offers CBCT imaging for patient setup. The currently used reconstruction technique contains a kernel-based scatter correction and a filtered back-projection algorithm. For TrueBeam, Varian Medical Systems commercially offers also an improved reconstruction technique – iterative CBCT (iCBCT), using a statistical reconstruction and a deterministic Boltzmann Transport Equation solver-based scatter correction. The advantages of iCBCT are improved soft tissue contrast and less noise. As it rewards projections with higher counts, effects from photon starvation, beam hardening and scatter are suppressed. Regularization reduces cone beam artifacts.

The statistical reconstruction and the improved scatter correction are evaluated at ProBeam. HU calibration, isocenter calibration, preprocessing and reconstruction parameters were optimized to achieve best results with this new reconstruction technique. A reduction of cone-beam, streak (Figure 1), shading artifacts and noise (Figure 2) was demonstrated during an early evaluation of iCBCT on ProBeam phantom scans and on clinical scans acquired during patient setup for daily treatment.

Iterative CBCT will also be implemented at ProBeam and ProBeam 360° to improve the image quality and facilitate faster and more precise patient setup. We expect this to bring enhancements of soft-tissue definition and better visibility for boundary definition for head/neck and pelvis cases equivalent to those shown in a study performed with TrueBeam at Henry Ford Health Systems. Potentially, the improved image quality will enable new applications like usage of CBCT images for replanning or adaptive radiotherapy on ProBeam.

PTC58-0023

Thermoacoustic range verification in the presence of acoustic heterogeneity and soundspeed errors: Accuracy and robustness relative to online ultrasound images

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Purpose: To experimentally demonstrate accuracy and robustness of thermoacoustic (TA) range verification relative to ultrasound images despite acoustic heterogeneity and discrepancies between assumed and true soundspeed. Prior results were for weak acoustic scatterers with known soundspeeds.

Methods: A beam sweeper was used to deliver 250 ns pulses at ANL's ATLAS facility. 0.26 Gy of 16 MeV protons and 2.3 Gy of 60 MeV helium ions were delivered to water and oil targets, respectively. TA signals were detected by a 96-channel ultrasound array (Fig. 1a), the processed to estimate range (Fig. 1b). The same soundspeed and transducer array were used to generate ultrasound images (Fig. 1c). An air gap phantom displaced the Bragg peak by 6.5 mm to demonstrate accuracy. The scanner's soundspeed setting was altered by to demonstrate robustness to soundspeed errors. Tissue mimicking gelatin and a bone sample were introduced to demonstrate robustness to acoustic heterogeneity (Fig. 1d).

Results: Single ion pulse measurements sufficed during the helium run, but signal averaging was required for protons. Estimates of the entry point agreed with the air-target interface in ultrasound images and range estimates agreed with TRIM simulations to within microns, even when TA emissions traveled through a strong acoustic scatterer. Estimated Bragg peak locations were translated 6.5 mm by the air gap phantom and correctly identified scenarios when the beam stopped inside bone.

Conclusions: Soundspeed errors dilate and acoustic heterogeneities deform ultrasound images. TA range estimates are transformed similarly and are robust relative to ultrasound images of underlying anatomy.

PTC58-0309

Estimating a proton's position in a pencil beam for proton imaging

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List mode proton imaging relies on the accurate estimation of each proton's trajectory through the imaged object. In most studies, two sets of position sensitive detectors preceding and following the object are used to compute the protons' most likely path (MLP). A simpler setup would be to omit the front trackers and rely rather on information from the beam delivery system of pencil beam scanning proton therapy.

In this work, we apply the Bayesian MLP framework to estimate the initial position of incoming protons, from the beam's mean position and measurements of the position/direction where the proton escapes the object. To simplify the calculations, we propose a linear projection model (LPM) that parametrizes the Bayesian calculations to estimate the optimal entrance position. From this, a cubic spline path (CSP) approach yields the full estimated path through the object.

The obtained uncertainty on the entrance position is significantly improved compared to the naïve approach of applying the pencil beam's mean position. In addition, the uncertainty is independent on the beam spot size when the spot size is above 4 mm (for a 16 cm object). The LPM yields similar results compared to the Bayesian MLP, when applied on different imaged objects and beam configurations, with significant improvements in speed and ease of implementation.

In conclusion, the method presented in this work serves as a simple and efficient way to estimate the proton trajectory in single sided list mode imaging setups at no loss in accuracy compared to the Bayesian MLP formalism.

PTC58-0639

Analysis of deformations in CBCTs and their effect on proton dose coverage in mediastinal thoracic patients

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In this retrospective planning study, the changes in anatomy as measured from CBCTs are compared to dose coverage of proton double scattering plans (DS).

We selected fourteen thoracic cancer patients who received a planning CT (PCT) as well as several CBCTs. Level 7 lymph nodes (LK7) were additionally contoured by experienced oncologists on PCTs and were propagated to CBCTs. Contours on CBCTs were evaluated using the dissimilarity coefficient (DIC), shift in the center of mass (3Dshift) and the maximum isotropic margin expansion (IME) of the initial LK7 on PCT which could enclose LK7 on CBCTs. DS proton plans were designed for LK7 on PCTs. The plans were perturbed for $\pm$5mm shift in isocenter and $\pm$5% density. Dose coverage failure was defined as $>\pm$5% change in the $D_{95\%}$ of LK7. This was tested for each field and each perturbation. If a dose point failed, re-planning was undertaken. The plans were afterwards projected on CBCTs and $D_{95\%}$ was analyzed for each field separately. In total, 10 fields were analyzed on 14 PCTs and 147 CBCTs.

172 out of 1470 analyzed points failed despite optimizing the plans for 5mm/5% perturbations. IME, 3Dshift and (1-DIC) are strongly inter-correlated. Correlation between $D95_{\%}$ and 3Dshift was significant (P=0.0076). Additionally, >50% dose points failed for 3Dshift $>$ 4.5mm, IME$>$ 4.9mm, and DIC $<$ 0.56(see fig1).

In conclusion, plan perturbations do not guarantee sufficient dose coverage in central thoracic tumors. Additionally, geometrical analysis of targets is a good indicator for DS dose coverage.

PTC58-0465

Intracranial immobilization evaluation at the Normandy Particle Therapy Center

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Introduction: The Normandy Particle Therapy Center started treating patients with intracranial and base of skull (BoS) tumors in July 2018. Data were analyzed for the first 20 patients who have completed their treatment.

Methods: The ProteusOne solution (IBA) includes a robotic couch (Leoni) coupled with a BoS frame (QFix) and a stereotactic imaging system. For each patient, the image guided repositioning protocol is the following: setup images to position the patient, beam images if any movement is applied to the tables. Treatment positions are considered acceptable if below 0.5mm within all directions and 0.5° in rotations. About 20 patients finished their treatments so far, representing above 3000 images. About 1800 represent the first images of either setup and beam images. Their corresponding correction vectors were analyzed.

Results: On the setup beam, the maximum mean deviation was 2.9 mm (in one direction) and the maximum standard deviation of 4.1mm, showing the need of image guidance at this critical stage of treatment. The maximum mean 3D vector was at beam position of 0.9mm with a maximum standard deviation of 0.9mm, and 0.5° in rotation ($\pm$0.4°).

Conclusion: These results show the excellent repositioning of the patient and the table close to the table limits (about 0.6mm 3D vector). Even without application of these corrections, this study shows that patient treatments would be within the planning tolerances of $\pm$3mm for intracranial/BoS tumors. As first patients are highly selected, further studies are required for better treatment delivery and quality, such images will be still performed.

PTC58-0408

Improving single-event particle imaging by ΔE-E filtering

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In single-event particle imaging, removing nuclear interaction events is crucial for accurate relative stopping power (RSP) reconstruction. Additionally, when imaging with ions, secondary fragments have to be separated from the primary histories. In this work, we investigated the use of additional ΔE-E filtering in helium CT (HeCT) and proton CT (pCT) with the prototype scanner developed by the U.S. pCT collaboration.

Experimental HeCT scans of various phantoms were obtained with the scanner at the Heidelberg Ion-Beam Therapy Center. Additionally, simulated HeCT and pCT scans were generated based on the prototype using the TOPAS toolkit. To remove secondaries and nuclear interactions which occurred within the detector geometry, the scanner 5-stage energy/range detector was adapted as ΔE-E telescope: A filter was generated from the parametrized ΔE-E pattern of primary particles and added to the current reconstruction procedure.

For HeCT, the additional ΔE-E filter removed the large systematic fluctuations otherwise present in the reconstructions (Fig. 1). With the filter, both simulated and experimental HeCT yielded a mean RSP accuracy better than 0.5% (Fig. 2). For pCT, the ΔE-E filter effectively removed systematic artifacts, which were similar, but less pronounced than observed in HeCT.

In conclusion, ΔE-E filtering improved the visual quality and RSP accuracy of both HeCT and pCT. To our knowledge, we present the most accurate single-event HeCT images to date.

PTC58-0392

Daily CBCT further reduces setup uncertainties for particle therapy- KS-CGMH initial experience

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Purpose: Setup uncertainty is critical for precision radiation therapy, especially for particle therapy. This study was conducted to evaluate the value of routine use of CBCT during patients' daily setup in a newly opened particle therapy center.

Materials and Methods: The Proton and Radiation Therapy Center at Kaohsiung Chang Gung Memorial started operation in October 2018. There are three 360-degree-gantry rooms for scanning beam delivery and all are equipped with cone-beam computed tomography (CBCT). During daily treatment, patients were immobilized with thermoplastic cast and/or vacuum bags. Additional customized accessories may also be used for better fixation. Since CBCT offers rotational adjustment and hence better setup evaluation, our institutional image-guidance protocol for intensity-modulated proton therapy (IMPT) requires routine use of CBCT after two orthogonal films (2D) adjustment. This retrospective study analyzed our initial experience of setup error values generated by CBCT after careful 2D adjustment.

Results: Between Nov. 2018 and Jan 2019, there were total 8 patients and 76 IMPT treatment sessions treated in our institution. The setup error values generated from daily CBCT after 2D adjustment were 0.83±0.69mm, 0.91±0.79mm, and 1.26±1.51mm (Mean±SD) with the maximum value of 3.94mm, 4.12mm, and 11.18mm in X-, Y-, and Z-axis, respectively. The corresponding rotational variation for yaw-, pitch-, and roll-axis were 0.35°±0.38°, 0.51°±0.48°, and 0.56°±0.47° with the maximum value of 2.23°, 2.18°, and 2.17°.

Conclusion: Our results demonstrated 2D evaluation offers acceptable setup results while CBCT could further reduce possible setup errors, both for translation and rotational errors. Further large-scaled and site-specific evaluation on the use of CBCT is warranted.

PTC58-0513

Implementing a CT for 3D IGRT at the isocenter at the Heidelberg Ion-Beam Therapy Center

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Introduction: At HIT patients are treated with carbon ions and protons in three treatment rooms. The high precision of particle therapy demands accurate image guided radiotherapy (IGRT). In cases where 3D IGRT was necessary, an ex-room CT and shuttle system were used. To reduce treatment time and positioning uncertainty, a 3D IGRT solution at the isocenter was developed.

Methods: Selection criteria for the CT were: Adequate soft tissue imaging, readiness for adaptive treatment planning, compatibility with the existing treatment table, low noise, small size, connectivity and mobility. Consequently, a mobile intraoperative CT was selected (Airo mobile TruCT, Mobius Imaging, USA, fig. 1). Key features are its wide bore (107 cm), small footprint (1.5 m^2) and mobility. Its 32-slice helical detector scans a range of 100 cm with 50 cm FOV in 42 seconds.

Results: Procedures for precise positioning of the CT at the isocenter via a moveable stage were developed (fig. 2). Special attention was paid to the high weight (816 kg). Acquisition modes were analyzed with phantom scans. Protocols were developed to achieve suitability for heavy ion treatment planning. The resulting CT scans were investigated for use in adaptive treatment planning. Existing workflow and QA procedures were expanded to accommodate for safe and efficient usage of device and data. Finally, prior to approval for treatment, a risk assessment was performed.

Conclusion: The existing HIT system was successfully upgraded to 3D IGRT at the isocenter. Next challenges are the derivation of a correction vector and usage in the gantry treatment room.

PTC58-0369

Dual-energy computed tomography improves delineation in primary brain-tumor patients

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Purpose/Objective: Dual-energy CT (DECT) improves the accuracy in proton therapy compared to single-energy CT (SECT). Since delineation of tumors and organs-at-risk (OARs) is gaining importance, we assessed whether DECT reduces the intra- and inter-observer delineation variability.

Material and Methods: Two cohorts of 10 primary brain-tumor patients each, scheduled for adjuvant radio(chemo)therapy, receiving either 120kVp SECT or 80/140kVp DECT with identical dose, were evaluated. Four different pseudo-monoenergetic CT (MonoCT) datasets, representing several contrasts, were derived from DECT. Three radiation oncologists delineated the postoperative tumor bed volume (TBV) and several OARs. Delineations on SECT datasets were repeated once to assess intra-observer variability. Finally, delineations were performed on T1/T2-weighted MR scans as clinical reference. The contour conformity was quantified by Jaccard index (JI) and Hausdorff distance (HD) between the contour intersection and union (Fig.1).

Results: The median inter-observer TBV conformity (Fig.2A) was almost independent from CT acquisition (HD=6-9mm/JI=61-66%) and comparable to MR (HD=6-7mm/JI = 66-67%). The consistency of brainstem contours (Fig.2B) was best at the lowest energy (median HD=2.8mm/JI=81%). The conformity of parotid glands (Fig.2C) gained slightly from higher energies (0.6mm median HD reduction, 1% JI increase) and led to better results compared to MR. Smaller inter-observer variations were mostly achieved using the most suitable MonoCT instead of SECT. The intra-observer TBV variability did not depend on clinical experience. However, less-experienced clinicians are more affected by different tissue contrasts (Fig.2D).

Conclusion: For primary brain-tumor patients, DECT-derived MonoCT datasets improve intra- and inter-observer delineation conformity compared to SECT. Moreover, they in part led to similar or better results as the gold standard MR.

PTC58-0404

An MRI study of organ shape variations between upright, reclined and recumbent positions: Implications for compact gantry-less particle therapy

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Purpose: A more compact proton therapy system could be achieved if the gantry could be removed. However, moving patients into different positions may be needed to replicate different beam angles for optimal treatment planning. The shift of the internal organs between positions poses a potential problem for CT scanning/simulation and treatment planning. In this study, we imaged a volunteer using FONAR Upright MRI to gain insight into the practical treatment of patients without a gantry.

Method: Head-and-neck images were taken in an upright sitting position (tilted 6° from vertical) and a recumbent position. Abdominal images were acquired in an upright posture, tilted 30° from vertical, and recumbent (Figure 1). For head-and-neck imaging, we used a 2-point Dixon sequence. For abdominal imaging, we used a bSSFP sequence with breath holding at both end of inspiration and expiration. Rigid ROI-based registration was subsequently applied and verified manually.

Results: Head-and-neck image registration showed that brain is aligned well between two positions, while the neck region exhibits postural deformation (Figure 2(a)). If one were to treat neck region, a separate registration could be done based on C-spine. Abdominal images showed a shift up to 1.3 cm between the organs and body surface when comparing sitting to reclining at 30° (Figure 2(b)-(c)).

Conclusion: The magnitude of the organ shifts observed between different positions can be included in treatment planning, measured with on-board imaging and corrected with adaptive planning. Together with the incorporation of immobilization, this study shows that compact gantry-less proton therapy system is a practical possibility.

PTC58-0464

Neutron detection for in-vivo range verification in intensity modulated proton therapy for prostate cancer

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Introduction: Uncertainties in the proton range in tissue during proton therapy limit the precision in treatment delivery, leading to increased margins and non-ideal field arrangements. Aiming to reduce these uncertainties, we have investigated a novel approach of exploiting the detection of secondary neutrons to monitor the beam range during proton therapy.

Materials and Methods: Neutron detection for in-vivo range verification was explored for proton beams in a water phantom and an intensity modulated proton treatment plan for prostate cancer, using FLUKA Monte Carlo simulations. Neutrons produced during delivery were tracked and detected for reconstruction of the neutron production distribution in the patient, based on a detector concept consisting of a hydrogen-rich converter followed by two position sensitive detectors. Finally, the neutron distributions from MC-ground truth and from reconstruction were used to estimate *range landmarks* which can be correlated to the proton range, and thus detect potential range shifts.

Results: The results indicate that the reconstructed neutron production position distribution and the associated *range landmark* are dependent on, and can be correlated to, the proton beam range. For the water phantom, range could be monitored with uncertainties of 2 mm or below for beam intensities as low as $5x10^7$ protons. Preliminary results from the patient plan indicate that similar results may be achievable in clinical scenarios.

Conclusion: The proposed secondary neutron detector concept is a promising alternative for in-vivo range verification in proton therapy, showing potential of range monitoring with millimetric precision during treatment.

PTC58-0082

Imaging tumor motion by the proton radiography technique based on energy-resolved dose measurement

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Purpose: Proton radiography (pRG) could improve treatment of mobile tumors with beam's eye view target alignment and water equivalent path length (WEPL) verification. We explored a method for imaging tumor in motion by the pRG technique based on energy resolved dose functions (ERDF) measured using X-ray flat panels.

Methods: A 228.9 MeV proton beam through a range modulator wheel provided the energy modulated broad beam for imaging and the ERDFs for deriving the WEPL values were acquired with a PaxScan 4030CB panel. Imaged objects included motion phantoms and a Gammex CT-calibration phantom containing tissue substitutes with known WEPL values. Various modulator wheel frequencies were explored from 0.3 to 3 Hz, with the fastest ERDF acquisition time of 333 ms per pRG frame, comparable to one-tenth of human respiration period. Accuracy of the obtained WEPLs for the Gammex tissue substitutes were evaluated. pRG images for motion phantoms were derived from both raw ERDF data and reconstructed ERDFs by phase-based sorting (Fig. 1) over multiple motion periods. Fig. 2 shows an example of pRG images for four phases of a metronome oscillating at 5s period.

Results and Conclusions: The 333 ms acquisition time produced WEPLs with larger uncertainties and poor pRG image quality, because it allowed only ~10 data points per ERDF, insufficient to specify the function uniquely. The frame rate of the panel (30Hz) is thus too slow to directly image tumor motion in real time, although ERDF sorting over multiple motion periods could improve pRG quality significantly.

PTC58-0336

Experimental validation of a dual-layer computed tomography method for reducing range uncertainty in proton therapy

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Purpose: To demonstrate the improvement of dual-layer CT (DLCT) over conventional single-energy CT (SECT) in estimating the proton range by tissue surrogate and animal tissue experiments.

Methods: We propose a method based on virtual monoenergetic 70 and 100keV images of DLCT for estimating proton stopping power ratios. Because children and adolescents have various bone tissues in the $8 \leq Z_{eff} \leq 10$ range, previously disregarded 42 pediatric ICRU tissues were added to 31 adult tissues for fitting the effective atomic number-mean ionization potential (Z_{eff}-I_m) curve. The SECT approach for comparison follows the clinical standard utilizing the stoichiometric calibration curve. Measured proton water equivalent range (WER) of 221MeV spot scanning beams passing through 12 types of tissue surrogates and fresh animal tissues were compared to calculated WER in the treatment planning system.

Results: Z_{eff}-I_m curves with or without pediatric tissues differ obviously in the $8 \leq Z_{eff} \leq 10$ range (Fig. 1). Percentage deviations from measured WER were reduced with the DLCT method for both surrogate and animal tissues (Fig. 2). By grouping animal tissues into categories of lungs, soft tissues and bones, their corresponding deviations were 2.9%, 0.85% and 1.28%. Because no animal tissues were within Z_{eff}=8-10, calculated WER with two Z_{eff}-I_m curves were not apparently different. The observed distal dose difference in pediatric pelvic tumors ranged from lowest value to 2.4% comparing the two curves.

Conclusions: Reduced errors in range estimation with DLCT were demonstrated. Using Z_{eff}-I_m curves based on adult tissues may lead to dosimetry differences in pediatric patients.

Physics: Image Guidance Poster Discussion Sessions

PTC58-0651

Distribution of patients which can be imaged with 235 MeV protons for radiography and computed tomography

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Purpose: To understand the percent of proton radiation patients that can be imaged by proton radiography or proton CT at proton centers having maximum energy of 235 MeV.

Methods: Our Python program reads in DICOM x-ray CT files and calculates the water equivalent thickness (WET) of rays diverging from a central beam axis. For radiography, the axis is defined by the treatment beam gantry and couch angle. For proton CT calculations, the WET values of diverging rays are computed along 18 different gantry angles ranging from 0 to 180 degrees with a zero-degree couch angle.

Results: The WET distribution was calculated for a sample of 729 patients from Northwestern Medicine Chicago Proton Center. The patients were then further subdivided into three anatomical regions: head/neck/brain, torso, and pelvis. The percent of head patients that can be imaged with 235 MeV protons is 97% for radiography and 99% for CT. The percent of torso patients that can be imaged with proton radiography is 95% and proton CT is 61%. The percent of pelvic patients which can be imaged by proton radiography is 7% and proton CT is 2%.

Conclusions: Over 95% of patients treated in the head, neck and torso regions can be imaged with proton radiography along the treatment beam axis. In addition, almost all the head and neck patients and over half the torso patients can be fully imaged with proton CT. Conversely, very few pelvic patients can be imaged with proton radiography or CT.

PTC58-0076

Feasibility of beam-on spot-by-spot PET-based range verification

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Objective: Range error detection on a short timescale provides a fast trigger for corrective strategies in proton therapy. Conventional PET-based verification precludes such immediate feedback. Previous studies[1,2] show the feasibility of in-beam PET monitoring using ^{12}N ($T_{1/2} = 11$ ms). We report on the range measurement accuracy for delivery of single spots by imaging the ^{12}N activity.

Methods: PMMA targets were irradiated for 60 s with a 150 MeV proton pencil beam consisting of a series of pulses of 10 ms beam-on and 90 ms beam-off. Two modules of a Siemens Biograph mCT PET scanner were used to image the beam-induced PET activity during the beam-off periods (Figure 1). ^{12}N images were reconstructed following Buitenhuis et al[2]. Relative range shifts in different scenarios were assessed for 10^8 and 10^9 protons per pulse.

Results: Using data from the first ten pulses for each irradiation with 10^8 protons per pulse, shifts of the target by 3 and 6 mm yield mean shifts in the ^{12}N activity profile of 3.5 $\pm$ 3.5 mm and 4.4 $\pm$ 3.4 mm respectively while for the irradiations with 10^9 protons per pulse, shifts of 4.7 mm and 9.8 mm were observed as 4.3 $\pm$ 1.9 mm and 8.6 $\pm$ 1.8 mm shifts respectively (Table 1).

Conclusions: Intra-fractional range errors could be determined with millimetre precision with a small fraction of the planned dose.

References: *P. Dendooven et al. (2015), Phys. Med. Biol.*,60(23), pp.8923-8947 *2. H.J.T. Buitenhuis et al. (2017), Phys. Med. Biol.*,62(12), pp.4654-4672

PTC58-0380

Experimental validation of DECT based proton range prediction in inhomogeneous animal tissues using high resolution gel dosimetry

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Dual-Energy computed tomography (DECT) is expected to allow for more accurate proton therapy treatment planning by improving the estimation of relative stopping power (SPR) and other tissue properties.

In this study, we investigated the accuracy of SPR prediction and tissue segmentation based on dual- and Single-Energy CT (SECT). For this purpose, fresh animal tissue samples were irradiated in a clinical proton therapy facility and high spatial-resolution three-dimensional proton dose distributions were obtained using dosimetric polymer gel downstream to the samples [1].

The accuracy of this setup was benchmarked against depth-dose measurements obtained with an ionization chamber behind an adjustable water column (peakfinder, PTW, Germany). The predicted SPR values showed good consistency for both methods with deviations below 1% (table 1).

DECT (90/150 kVp) and SECT (120kVp) images were acquired and converted to SPR and tissue compositions as input for MC-simulations (figure 1). DECT-to-SPR conversion yielded mean errors of 0.5%, outperforming the SECT calibration with 1.1% deviation from peakfinder results. A detailed comparison of measured dose distributions to MC-simulations for highly inhomogeneous samples will be presented.

In summary, dosimetric gel was used to obtain 3D high-resolution proton ranges and compared to peakfinder measurements and MC-simulations, in order to quantify the accuracy of DECT and SECT based tissue characterization. [1] Hillbrand et al, Z Med Phys., 2018 [2] Saito M, Sagara S, Med Phys. 2017. Acknowledgements: DFG (GRK 2274, MAP); Sandy Ebert; Fabian Doerringer; Christopher Kurz

PTC58-0565

Optimizing image quality of single-sided list mode particle imaging

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Precise list mode particle imaging relies on accurate reconstruction of the particle most likely path (MLP) through the patient. This requires two sets of position sensitive trackers, one preceding and one following the patient, resulting in additional material in the beam line during irradiation and increased complexity of the clinical environment. In this work we investigate single-sided particle imaging by omitting the front trackers and propose a method to optimize the image quality for such a setup by combining two opposing radiographies.

The GATE Monte Carlo toolkit was used to simulate a pencil beam scanning system irradiating simple geometries and updating the particle MLP with pencil beam information substituting the front trackers. This come at the cost of reduced spatial resolution via deterioration of MLP estimations exemplified in *Figure 1*.

Combining two opposing radiographies separated by a 180° angle, each reconstructed using only the more accurate latter half of the particle MLP, show a significant improvement in spatial resolution compared to original single-sided particle imaging using the full MLP, illustrated in *Figure 2*.

Assigning a different weight to one opposing image can additionally allow for further improved image quality around features of interest close to one end of the phantom. This combination of two opposing radiographies is foreseen to be useful in CT-imaging where the opposite 180° rotated image is already available from scanning and will aid in bringing particle imaging closer to clinical reality.

Physics: Monitoring and Modelling Motion
PTC58-0181

Measurement of energy loss of secondary charged particles for 12C-ion pencil-beam radiotherapy monitoring

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The highly localized dose deposition of carbon-ions makes them an attractive tool for radiotherapy. At the same time, it entails higher sensitivity to dynamic geometry changes during the treatment. Therefore, in-patient monitoring techniques for carbon-ion beam delivery are of interest.

The monitoring method investigated in this contribution is based on the detection of the secondary charged nuclear fragments emerging from an irradiated target. We investigated the benefits of the knowledge of the fragment's energy-loss information acquired in thin silicon-detector layer. In particular, the correlation between the measured depth of the fragments' origin and the planned carbon-ion range was of interest.

In order to mimic a clinical treatment, a typical 12C-ion treatment plan fraction of a head tumor was applied on an anthropomorphic Alderson head phantom at the Heidelberg Ion-Beam Therapy Center (HIT), Germany. The directions of the emerging secondary ions were measured by a pair of pixelated silicon detectors Timepix3 (TPX3), developed at CERN. These detectors were also used to measure the ions' energy deposition in the sensitive layer.

We found that there are significant differences in the ions' track origins for different energy depositing ions. The energy deposition of single detected secondary-ions in TPX3 detectors is thus linked to the secondary-ion's velocity, and this way, to the fragmentation depth. This additional information can therefore be used in the future to improve the precision of the 12C-ion pencil-beam monitoring based on secondary charged ions.

This demonstrates the potential of using secondary-ion energy-loss for pencil-beam range monitoring method.

PTC58-0530

Evaluation of the septal penetration and scattering on the range quantification in protontherapy in the gamma camera: The GEANT4 study

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The range uncertainty is one of the limiting factors in the use of protons in radiotherapy. One of the promising methods for range verification to overcome this limitation is the use of Knife Edge slit camera based on prompt gamma imaging. Due to the high energy of prompt gammas, in this cameras, septal penetration and scattering could have an effect on quantification of the range. At this study, the effect of these parameters on the obtained range from the camera was evaluated. The simulation was performed using the GEANT4 toolkit. The Knife Edge camera characteristics extracted from the available references. The detection profiles were considered for point and linear photon sources with energy of 4.4 MeV and for prompt gammas induced during the PMMA phantom irradiation with 230 MeV energy protons. Detection Profiles with and without considering the septal penetration and scattering obtained for 2, 5, 10, 15 mm displacement; the range calculated for different situations. It was observed that neglecting the penetration and scattering in the septal leads to an underestimating the absolute value of the range up to 5 mm in measurements with 1-2 mm standard deviation for 10^9 particle history in simulation. This difference varies according to the type of source, detection energy window, and amount of source displacement in realistic Knife Edge slit camera. It was also determined that, If the system considered to be ideal, the estimation of the range is independent of the mentioned parameters.

PTC58-0279

Improvement of retrospective sorting for artefact reduction in 4DMRI of the abdominal site

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Introduction: 4DMRI for organ motion management in external beam radiotherapy is increasingly gaining importance to support 4DCT. This work aims to investigate strategies to reduce 4DMRI sorting artefacts in abdominal cancer patients treated with carbon-ion therapy.

Methods: Multi-slice 2DMRI were acquired for 6 patients (25 sagittal slices, 30 frames each, 1.33x1.33x5mm resolution) and a retrospective 4DMRI sorting method based on k-medoids clustering was implemented. Anatomical features were extracted through SIFT algorithm and tracked using template matching. Filtering of outlier trajectories was evaluated with three different approaches: (i) single clustering, which divides features in a fixed number of clusters; (ii) iterative clustering, which splits the features in two groups and repeats the process on the largest for a fixed number of iterations; (iii) correlation, which groups features together based on mutual correlation. The most populated cluster/group of trajectories is used for 4DMRI reconstruction. Artefacts were quantified in each reconstructed volume through the RMSE between the kidney upper profile and a polynomial fitting curve. The three 4DMRI reconstructions were compared with the reconstruction with no filtering.

Results: The reconstruction with no filtering resulted in higher RMSE compared to the others (fig.1) and, although not significantly different, the reconstruction using correlation filtering presented the lowest RMSE, as well as less image artefacts (fig.2).

Conclusions: Preliminary results suggest the filtering algorithm based on correlation as a promising approach in limiting 4DMRI artefacts. Further investigations will rely on extending the testing dataset, which may result in significant statistical differences, and on evaluating 4DMRI clinical relevance.

PTC58-0481

Dosimetric impact of interfraction motion on Proton PBS treating prostate with pelvic lymph nodes with different image guidance strategies

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Introduction: To evaluate dosimetric impact of real patient interfraction prostate motion on proton PBS treatment of prostate with pelvic lymph node using different image guidance strategies.

Material and Methods: Five prostate patients treated with pelvic nodes using PBS were selected for the study. Real interfraction prostate motion data were used to generate a total of 12 organ motion scenarios in Raystation. The maximum motion were 0.7cm, 1cm and 0.8cm in the LR, SI and AP directions, respectively. Three image guidance strategies were evaluated using the 12 datasets: bony matching, seed matching and hybrid matching. In bony matching, dose was recalculated on deformed datasets with planned isocenter; in seed matching, dose was recalculated on deformed datasets with shifted isocenter following prostate motion; in hybrid matching, when prostate interfraction motion magnitude beyond the pelvic node PTV margins, the extra displacement was split between seeds and bony. Dose to the prostate and pelvic node CTV and OARs were calculated and presented for all 3 strategies.

Results: For bony matching, prostate CTV dose degradation was prominent for interfraction prostate motion beyond prostate PTV margins; for seed matching, pelvic node CTV dose degradation was prominent for interfraction prostate motion beyond pelvic node PTV margins; hybrid matching mitigated the dose degradation to pelvic node CTV with no significant dose degradation to prostate CTV.

Conclusions: Interfraction prostate motion from pelvic node is a crucial part of the prostate and pelvic node PTV margins, which is directly related to image guidance strategies during proton PBS treatment.

PTC58-0143

A new transparent beam profiler based on secondary electrons emission for hadrontherapy charged particles beams

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Beam profiling during patient treatment in hadrontherapy requires ultra-thin monitors to preserve the high beam quality. For detectors upstream in the line, a material budget as low as $\sim$15 μm water-equivalent is needed. In addition, the current trend of dose escalation to treat highly resistant tumors implies challenging requirements to monitor radiation hardness and dynamic range.

We propose a new type of beam profiler, PEPITES, using secondary electron emission (SEE) and built with thin-film techniques. The beam is profiled by crossing nanometric patterns which emit the SEE signal. The patterns are deposited on polymeric membranes, which, in contrast with conventional systems like ionization chambers, are free from mechanical constraints and can be as thin as achievable.

The thinness of the monitor disturbs very little the incident beam, which can then be delivered to the end user while keeping the profiler in the line, ensuring continuous monitoring. Also, it makes the energy loss very small and consequently the associated damage, allowing the extension of the profiler operating time.

A simple prototype has been successfully operated with proton and alpha beams at the ARRONAX cyclotron in a wide range of currents (100fA - 100nA) and for several energies. Secondary electrons yields have been measured, and irradiation damages have been evaluated with regards to the deposited dose. Optical spectroscopy and surface microscopy tools have been used to characterize the damages induced in the polymer.

We will present the performance of the detector and its assets for the beam monitoring in hadron therapy.

PTC58-0162

Comparison of signal transduction latency with different types of respiratory sensor in respiratory gating system to gate scanning proton beam

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Purpose: Our proton therapy system is equipped with the Anzai respiratory gating system. There are two types of respiratory sensors - a patient contact type (Load Cell Sensor) and a patient non-contact type (Laser Sensor) - in this gating system. Since temporal accuracy of interlocking from sensing respiratory motion to gating scanning proton beam on or off is very important in proton therapy, this study aimed to compare the signal transduction latency with different types of respiratory sensor.

Materials and Methods: We used CIRS Dynamic Thorax Phantom to simulate respiratory motion. Five seconds of one respiratory cycle and 30 mm of respiratory motion were set. We acquired images and waveform data of respiratory motion by 4D computed tomography and Anzai respiratory gating system with different types of respiratory sensor. We adopted Level to Level Mode to gate scanning proton beam, and allowed beam on during threshold waveform level. We recorded the signal transduction latency from sensing respiratory motion to gating beam on or off with different types of respiratory sensor to compare the temporal accuracy of interlocking.

Results: With Load Cell Sensor, the signal transduction latency from sensing respiratory motion to gating beam on or off was around 20 milliseconds. Likewise, the signal transduction latency with Laser sensor was around 20 milliseconds, too. Both types of respiratory sensor fulfilled the requirement ($<$100 milliseconds) of annual quality assurance of respiratory gating in Task Group 142 report.

Conclusion: There was no significant difference of signal transduction latency between Load Cell Sensor and Laser Sensor.

Physics: Adaptive Therapy

PTC58-0351

Towards interventional particle therapy for advanced cancer care

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The high precision of particle therapy (PT) comes as a double-edged sword, since PT is usually less robust than conventional radiotherapy. Several different uncertainties can have a significant impact on the final dose delivery.

The clinical workflow in PT has been adopted from conventional X-ray radiotherapy, where the treatment plan is based on the initial CT scan of a patient. A Europe/US/Asia group of clinics, institutes and industry has started collaboration as Real-time Adaptive PT of Cancer (RAPTOR). RAPTOR strives to create flexible and ideally real-time PT treatment, which would in the future combine imaging, planning, quality assurance and irradiation in real-time.

RAPTOR will focus on three main topics and initially bring daily adaptive treatment into the clinic. The topics are adaptive intervention, in-vivo treatment verification and integration - schematically presented on the figure. Adaptive intervention will develop interventional delivery, which will include adjustable optimization of treatment plan, rapid quality assurance and flexible beam delivery. In-vivo treatment verification will ensure an unambiguous treatment verification with dedicated PT imaging, range measurements and dose accumulation. Within RAPTOR initiative there are already experts on specific topics mentioned and RAPTOR will be working on a seamless integration and appropriate validation of the whole framework to the clinical environment.

In order for the framework to succeed a wider agreement within PT community is required. Therefore, RAPTOR initiative would like to present its ideas and hopefully get new partners, such as other PT users and vendors, for successful implementation of RAPTOR framework into the clinic.

PTC58-0430

Can we use deformable image registration within Velocity to determine if a proton patient needs a replan?

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We retrospectively planned 5 head and neck patients delivering 70 Gy to the primary volume and 54.25 Gy to the elective volume over 35 fractions with protons. These patients had daily CBCT imaging allowing us to use Velocity (v4) to deform the planning CT (pCT) to the CBCT, creating an adaptive CT (aCT) that has the anatomy of the CBCT image and the electron density information of the pCT. The dose was recalculated on the aCT in Eclipse and relevant DVH parameters were extracted. The dose was accumulated weekly and recalculated on a repeat CT at fraction 9. The use of an in house CBCT shading correction algorithm was also investigated to compare with these values.

The D95% for the CTVs and PTVs are shown in Figure 1 (left) and the mean dose to the left and right parotids, oral cavity and larynx are shown (right) for a representative patient. The DVH parameter is shown for each fraction recalculated on the aCT. The dotted lines show $\pm 2\%$ from the baseline plan (fraction 0) and the dashed line the mean over all the fractions for that DVH parameter.

Over the 5 patients investigated so far with this method there were no patients that would have needed replanning. Deformable image registration in velocity was successfully used to estimate the impact of patient anatomical changes on proton treatment plan quality. A further 5 patients will be analysed and work investigating if less robust plans show more need for replanning will also be performed.

PTC58-0177

Predicting dose differences to swallowing OARs in head and neck cancer (HNC) patients

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Introduction: Differences between planned (D_P) and delivered (D_A) dose (Δdose) in HNC patients treated with X-Rays are poorly understood. Proton dosimetry may accentuate such differences. Quantifying and predicting these differences will help guide adaptive PBT strategies for HNC.

Methods: Two hundred thirty-nine HNC patients from VoxTox (UK-CRN-ID-13716) were included. All underwent radical IG-IMRT with TomoTherapy. Swallowing OARs (Ipsi & contralateral parotid & submandibular glands – IPG, CPG, ISMG & CSMG, superior & middle pharyngeal constrictors – SPC/MPC, oral cavity – OC and supraglottic larynx – SGL) were segmented on planning scans. Daily IG-MVCT images, in-house dose calculation software (CheckTomo) and deformable image registration (Elastix) were used to calculate D_A, for comparison with D_P. Hypothesised predictors (HPs) of Δdose including primary disease site, TNM, and pre versus final-week weight loss (WL) and separation reduction (SR) were measured. Univariate relationships between HPs and Δdose were assessed, with Bonferroni corrections.

Results: Mean WL was 6.3kg (7.3%). Δdose (D_A - D_P, 95% CI) were: IPG 1.56Gy (1.37-1.74), CPG 0.94Gy (0.77-1.11), ISMG 1.24Gy (1.11-1.36), CSMG 1.17Gy (1.05-1.29), SPC 0.81Gy (0.71-0.91), MPC 0.68Gy (0.55–0.82), OC 0.44Gy (0.30-0.57), SGL 0.98Gy (0.78-1.17). PG Δdose was higher in nasopharynx primaries (Figure 1). SMG and SPC/MPC Δdose was greater in N2+ vs N0-1 disease, OC and SGL Δdose was greater in T3-4 vs T0-2 disease (Figure 2). No correlations with weight loss and Δdose were found.

Conclusions: Higher T&N stage predicts higher D_A to swallowing OARs. Nasopharynx patients are at greater risk of higher PG D_A. Greater weight loss does not predict dose differences.

Physics: Adaptive Therapy Poster Discussion Sessions

PTC58-0007

Anatomy change over the treatment course for non-small cell lung cancer patients and its impact on IMRT and PSPT deliveries

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Purpose: To quantify the tumor anatomy change of non-small cell lung cancer patients treated with passive scattering proton therapy (PSPT) and intensity modulated radiation therapy (IMRT) through 6-7 weeks of treatment, and analyze its correlation with the need to adopt adaptive radiotherapy (ART).

Materials and Methods: Weekly 4D CT sets of 32 patients (8/8 IMRT with/without ART, 8/8 PSPT with/without ART), were deformably registered to the planning CT. Anatomy change was quantified as the mean variations of CTV relative to the planning CT by averaging the magnitude of deformation vectors of all voxels within the CTV contour. Mean variations of CTV were compared between subgroups classified by adaptive status and treatment technology using independent T-test. Logistic regression analysis was performed to clarify the effect of anatomy change on the probability of ART adoption.

Results: There was no significant difference ($p=0.679$) for the time-averaged mean CTV variations from the planning CT between IMRT (7.61 ± 2.80 mm) and PSPT (7.21 ± 2.67 mm) patients. However, significant difference ($p=0.001$) was observed between adaptation (8.93 ± 2.19 mm) and non-adaptation (5.90 ± 2.33 mm) patients, when treatment modality was not considered. Mean CTV distance from the planning CT in all patients increases significantly ($p<0.001$), with a changing rate of 1.76 mm per week. The logistic regression model correctly predicted 71.9% of cases in ART adoption.

Conclusion: The magnitude of CTV variation over time could be greater than usual treatment margin. Mean CTV deviation from the planning position could be used to identify lung cancer patients that may need ART.

PTC58-0705

Water equivalent thickness from instantaneous proton radiographic transmission measurements

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A proton radiography system applied at a proton therapy treatment center could be utilized to provide instantaneous, beam's-eye-view feedback of patient anatomy, as well as a proton-based estimation of a patient's water equivalent thickness (WET). Here, a magnetic lens-based flash radiography system is implemented at an 800-MeV proton radiography center, in order to provide an estimation of the water equivalent thickness of an anatomic hand phantom. The system transmission is determined by the nuclear attenuation within the object, as well the design of the system, determined by a collimation cut angle based off of the multiple Coulomb scatter acquired in the object, according to the following formula:

A transmission radiograph is then converted to a water-equivalent thickness by inserting the known values for the nuclear interaction length and the radiation length of water. The transmission formulae can then be applied pixel-by-pixel to convert a transmission proton radiograph to an estimate of water-equivalent thickness areal density, in g/cm2. A transmission image and its accompanying WET calculation appear in Fig. 2 below:

Methods for scaling this system down from 800-MeV to a more standard 250-MeV system, for the purposes of estimating WET using this technique with clinically-relevant energies, will be described. The ability to calculate a patient's WET using proton radiography allows for the acquisition of a proton-CT that could be used for treatment planning, as well as an instantaneous feedback on WET from the beam's-eye-view perspective that could enable real-time adaptive proton therapy.

PTC58-0722

Aeration change and beam arrangement justify mid-treatment adaptation of proton treatment plans

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This study determines the impact of change in aeration in sinonasal cavities on the robustness of passive-scattering proton therapy plans in patients with sinonasal and nasopharyngeal malignancies. Fourteen patients, each with one planning CT and one CT acquired during radiotherapy were studied. Repeat and planning CTs were rigidly aligned and contours were transferred using deformable registration. The amount of air, tumor, and fluid within the cavity containing the tumor were measured on both CTs. The original plans were recalculated on the repeat CT. Dosimetric changes were measured for the targets and critical structures. Median decrease in gross tumor volume was 19.8% and correlated with the time of rescan. The median change of air content was 7.1% and correlated with the tumor shrinkage. The median of D_{mean} change was +0.4% for GTV and +0.3% for clinical target volume. Median change in D_{max} of the critical structures were as follows: optic chiasm +0.66%, left optic nerve +0.12%, right optic nerve +0.38%, brainstem +0.6%. The dose to the GTV decreased by more than 5% in 1 case, and the dose to critical structure(s) increased by more than 5% in 3 cases. These four patients had sinonasal cancers and were treated with anterior proton fields that directly transversed through the involved sinus cavities. The change in dose in the re-planning was strongly correlated with the change in aeration ($p=0.02$). We found that the change in aeration in the vicinity of the target and the arrangement of proton beams affected the robustness of proton plan.

Physics: 4D Treatment and Delivery

PTC58-0117

Variable cycle-based respiratory guidance method for target motion compensation in scanned heavy-ion beam radiotherapy

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For synchrotron-based scanned heavy-ion beam delivery, the beam extraction period varies with different energies due to the non-linear relationship between beam energy and range. To overcome inefficiencies and interplay effects between the target motion and the dynamic beam delivery process, we proposed a variable cycle-based respiratory guidance method to synchronize breathing patterns with synchrotron magnetic excitation patterns.

We collected the magnetic excitation waveforms (MEWs) under scanned beam delivery mode with 123 different energies form Heavy Ion Medical Machine (HIMM). With those MEWs, we built synchrotron magnetic excitation patterns and period-adjustable personalized guidance curve to synchronize the breathing pattern with the magnetic excitation patterns. The patients were guided to perform short breath holds (BH) with the aid of BFB system.

The purpose of this study was to evaluate the treatment precision and efficiency of the respiratory guidance method in scanned heavy-ion beam delivery mode. Using 192 respiration traces from eight healthy volunteers who were guided to perform short BHs under fixed cycle breathing guidance and variable cycle breathing guidance with the aid of BFB, a series of dedicated 4D dose calculations (4DDC) were performed on a geometric model.

Our results showed that with the fixed cycle guidance the dose homogeneity was destroyed even in conjunction with respiratory gating, as shown in figure 1 (a)∼1(c). However, the dose homogeneity was restored under variable cycle guidance mode, as shown in figure 1(d). Further study shows that with the variable cycle guidance method, the treatment efficiency is nearly doubled.

PTC58-0124

4DMRI-based investigation of the effectiveness of different gating approaches for pencil-beam scanning proton therapy of pancreatic cancer

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Abdominal organ motion leads to pronounced interplay effects in pencil-beam scanning particle therapy of pancreatic cancer. In this study, the mitigation of the resulting dosimetric impact by application of beam gating based on certain pre-selected gating criteria was investigated.

Based on patient-specific synthetic 4DCTs, generated from multiple 4DMRI and 3D planning CTs of 9 pancreatic cancer patients, we investigated the impact of different gating windows in a comprehensive 4D dose calculation study. The gating windows include fixed (5 mm) or relative (10%-90%) amplitude threshold values of CTV (clinical target volume) motion and 95% CTV overlap criteria. Additionally, gating with variable initial breathing phase, which is highly related to the first scan spot, was investigated. The interplay effect was quantified by the dose homogeneity index HI=d5/d95 in the CTV.

An effective interplay mitigation was observed for small gating windows with a linear relation between the size of the gating window and HI. Relative gating criteria showed better results than fixed threshold values or CTV overlap criteria. Figure 1 shows the dependency of HI on the number of fractions. For single fractions, less interplay effect was observed for all gated compared to non-gated scenarios. For multiple fractions, a sufficient mitigation of the interplay effect was assured by gating with variable initial breathing phase.

Gating is an effective option for particle therapy of pancreatic cancer, especially for large motion amplitudes or hypofractionated treatments, where less fractionation-induced mitigation of the interplay effect occurs. Variations of the initial breathing phase further improve the gating effectiveness.

PTC58-0206

Robust optimization in conformal 4D treatment planning for carbon therapy of lung tumors

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Conformal motion mitigation can be achieved by 4D-optimization of a 4D treatment plan library, which is synchronously irradiated to the respiratory motion. Multi-field optimization (IMPT) could further improve the conformity of such plans; however, internal field gradients make IMPT prone to dose degradation in the presence of uncertainties. We propose a 4D-robust optimization to mitigate this issue.

A voxel-wise worst-case method was introduced into the treatment planning system TRiP98, based on 9 possible scenarios, consisting of 1 nominal, 2 range (CT density ±3.5%) and 6 patient setup scenarios (±3mm in cardinal directions). Conformal 4D-optimization was compared for robust IMPT vs. conventional IMPT with 3mm isotropic margins. Plan quality was evaluated by robustness analysis based on 21 possible 4D dose distributions, including superposition of setup errors and range changes.

Feasibility was tested on a NSCLC patient with 5 lesions and motion amplitudes up to 17mm, with single fraction dose of 24Gy. Robust conformal 4D-optimization significantly reduced DVH uncertainty bands, significantly improved average D99% target coverage, while simultaneously fulfilling the dose volume constraint of the nearby smaller airways in all considered scenarios, compared to 90.5% of scenarios for the conventional case (see fig.1). Compared to the 4D-optimized ITV with robust IMPT, the increased conformity further reduced the smaller airways dose exposure.

For the considered patient, only robust optimization enabled sufficient target coverage, while providing superior OAR sparing simultaneously. Considering error scenarios during optimization enables to account for range changes beyond those already considered by 4D-optimization approaches.

PTC58-0209

Implementation and first tests of the CNAO dose delivery system at GSI

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Thoracic cancer survival rates continue to show limited improvements despite generally more effective cancer treatment modalities. Current dose delivery systems are not fully capable of handling realistic patient conditions, resulting in either significant side-effects of radiation treatments or failed tumor control from inadequately administered treatment plans. As surgical resection and chemotherapy are both limited in their applicability to thoracic cancers, and the precision of carbon ion therapy, in conjunction with synchronized delivery, via 4D Robust Optimization method could provide more effective treatments.

The CNAO dose delivery system was transferred and tested at GSI. The core functionality of the DDS, treatment delivery protocols and preliminary motion mitigation functionalities were experimentally investigated. The GSI DDS periphery performed as anticipated, including in synchronization of timing events, magnet interfaces, beam request software and beam monitors. DRAM based treatment plan handling has been developed. A motion monitoring system, capable of defining motion states guiding treatment delivery progression, has been implemented. Both beam gating –via RF knockout– and beam abort functionalities are essential for this, and have been developed and experimentally verified during Argon-18 test beams. Particle intensity measurements during fast gating tests reveal that beam deletion and recovery were nearly instantaneous (Figure 1). Further modifications can eliminate the residual particle intensities.

The integrated 4D-DDS capabilities will be verified during carbon and oxygen ion beam times, scheduled for February. Performed tests will include the multi-gating functionality, delivery synchronization via 4D-dose profile measurements and treatment disruption. The 4D DDS will ultimately be integrated into the CNAO clinical treatment system.

PTC58-0533

Dosimetric comparisons between breath-hold and non-breath-hold plans in intensity modulated proton therapy

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Purpose: The breath-hold technique can be used to mitigate target motion, to minimize the target margin and reduce the dose to normal tissues and the interplay effect with intensity modulated proton therapy (IMPT). The purpose of this study was to perform dosimetric comparison between breath-hold and non-breath-hold IMPT plans.

Methods: Twenty-three consecutive patients treated with a voluntarily breath-hold spirometry system (SDX, Dyn'R, France) were used for dosimetric analysis. All patients underwent a breath-hold CT set to 75% of deepest inspiration and a 4D-CT, with or without compression belts. Clinically acceptable breath-hold and non-breath-hold plans were created on respective simulation scans. Dose-volume histograms (DVH) of the two plans were compared for each patient.

Results: Patients had mediastinal/lung (n=7), liver (n=11), or upper abdominal (n=5) malignancies. As shown in Table 1, the average CTV of breath-hold scans, CTV1 (initial: 23 patients) and CTV2 (small field boost: 10 patients) were reduced to 70±23% and 68±23% of ITV1 and ITV2 of 4D-CT scans, respectively (Figure 1-A). Compared to non-breath-hold plans, the mean dose to liver, stomach, kidney, esophagus, heart, and V20 of total lung of breath-hold plans were reduced to 76%, 71%, 71%, 88%, 74%, and 81%, respectively (Figure 1-B and C). The small bowel, large bowel, heart, and spinal cord max doses were lowered to 80%, 56%, 93%, and 86%, respectively (Figure 1-D).

Conclusion: This study showed that breath-hold plans can significantly reduce the treated target volume and consistently lower the mean and maximum doses to the organs at risks by about 15-30%.

PTC58-0538

Beam delivery requirements for breath-hold treatments in a proton therapy facility

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Breath-hold (BH) can mitigate the interplay effect in proton pencil beam scanning treatments (PT) of moving targets. However, in order to avoid uncertainties related to non-reproducibility between different BHs and to make treatments more efficient, single field delivery within a single BH is desirable. Unfortunately, field delivery times in PT facilities are often too long for this goal.

To understand the impact of the different delivery dynamics on treatment times, these have been studied considering different tumor shapes with increasing complexity and volumes up to 500 cc. Both standard and hypo-fractionated treatments have been simulated using 0.6/3Gy field doses and using 3-fields/fraction plans. For all scenarios, treatment times for different dose rates, scanning speeds, energy switching times and scanning modalities (discrete and continuous line scanning) were compared. Calculations have also been experimentally validated using patient fields delivered on PSI Gantry2.

Increasing the dose rate does not fully compensate for dead-times. This is particularly true for energy switching times above 500ms. On the other hand, spot- and layer-reduction techniques, or fast delivery techniques, may additionally help to reduce the treatment time. For facilities with small dead-times, we found that an increase in dose rate by a factor 2-10 might be required to achieve treatment times of less than 20s, depending on the irradiation scenario considered.

In conclusion, a PT facility with fast energy switching could already treat small targets with a single BH, but higher dose rates are in general needed to achieve delivery times compatible with this goal.

PTC58-0546

Gating system for protons and imaging: Translating a research tool into a clinical product

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We present a compact optical motion monitoring system for time-resolved imaging and respiratory synchronised treatment delivery. Patient motion is derived from the position of the external markers enabling prospective and retrospective 4D CT, MR image acquisition and, ultimately, beam gating.

The solution is based on the Polaris optical localization technology (NDI, Waterloo, CA), and is designed to measure a breathing surrogate signal from surface markers placed on anatomical landmarks. Dynamic motion tracking accuracy has been measured as 0.18mm (IQR) at 60 Hz sampling rate. Developments have taken into account the requirements of risk analysis for clinical use, including the introduction of a dedicated hardware module for the continuous surveillance of system integrity and interfaces to proton radiotherapy machines. As part of the acceptance tests, the position measurement latency has been evaluated and found to be 16.6 $\pm$ 1 msec, with the digital output interface being updated at 1 kHz. Additional latencies of 41.1 $\pm$ 6 μs and 50 $\pm$ 6 μs have been observed when the system is used for beam gating when sending beam on and off requests respectively.

Preliminary tests have also been performed with the system in a 1.5T MR room. No artifacts were observed on images, and the optical tracking was not affected by the magnetic field. The system is expected to enter clinical operation on PSI Gantry 2 early in 2019 as a couch mounted gating system and motion monitoring system for 4D imaging and treatments (Figure 1).

PTC58-0702

A novel layer synchronization method can maintain target coverage and improve treatment efficiency in proton PBS treatment of moving tumors

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Purpose: Large respiratory motion can lead to significant dose degradation in PBS proton therapy in treating moving tumor. A layer synchronization (LS) method is proposed, intentionally delivering spots in regular rather than random patterns, to reduce the impact of motion and maintain the robustness of PBS proton treatment.

Method: Ten lung cancer patients with 4DCT are retrospectively studied. For each patient, 4D dose(4DD) is used to simulate 37-fraction treatment and the delivery starting point of each fraction has a random distribution within breathing phases. The total monitor units(MU) delivered in each CT phase is analyzed and the spot/MU distribution over the CT phases was defined as a spot/MU pattern(Fig1). For each fraction the spots dose on the corresponding phases was accumulated to the reference 4DCT phase(end-of-exhale) using 4DD.

Results: Study demonstrates that some MU patterns have poorer target coverage, while other patterns can achieve adequate coverage (Fig2(a-c)). As the target motion can be monitored during treatment, it can be used to trigger LS so that beam-on is synchronized to a selected MU patterns at designed breathing phase points. In most cases a-single-layer can be delivered within one breathing cycle, thus each layer can be split into 1$\sim$3 segments onto the adjacent phases ($\leq$3/8 of a breathing cycle). The total beam time will be determined by the number of layers, which can be equal to the treatment time of free breathing.

Conclusion: Spot delivery can be selected from one of numerous patterns. Thus, LS is very efficient to maintain target coverage in treating moving tumors.

Physics: 4D Treatment and Delivery Poster Discussion Sessions
PTC58-0236

A comparison of various scanned proton pencil beam delivery strategies for the treatment of moving targets

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Purpose: The treatment of moving targets with pencil beam scanned proton therapy (PBS-PT) relies on repainting strategies to smooth out interplay effects. PBS-PT machines, such as ProteusPlus (PPlus) and ProteusOne (POne), deliver a continuous or a pulsed beam, respectively. In PPlus, non- or scaled repainting can be applied, while POne implies intrinsic repainting due to its pulsed delivery. We investigate here the efficacy of these two machine characteristics for the treatment of thoracic tumors.

Materials and Methods: 4D robust optimised PBS-PT treatment plans were calculated for eight non-small cell lung cancer (NSCLC) patients. All plans were delivered in dry runs at PPlus (with and without five times layered repainting) and POne facilities to obtain machine log files. By using these log files and verification 4DCTs per patient (acquired at different time points), a 4D robustness evaluation was performed towards setup and range errors, machine errors, anatomy changes, breathing motion, and interplay effects. Plan robustness was then assessed through the resultant voxel-wise worst-case dose.

Results: Clinically relevant differences in voxel-wise worst-case dose distributions were observed between the PPlus and the POne plans (Fig. 1). In PPlus, repainting generally provided more robust plans. POne resulted in better target coverage than the PPlus repainted plans. A maximum voxel-wise worst-case V_{95}(CTV) improvement from 50.30% (repainted PPlus) versus 94.57% (POne) was observed for patient case Pt.5 (Table 1).

Conclusion: Repainting enables the mitigation of potential disturbing effects of PBS-PT for moving targets. The intrinsic repainting of POne showed to be more effective than the scaled repainting of PPlus to treat NSCLC.

PTC58-0367

Head and Neck IMPT robustness evaluation using dose accumulation and TCP/NTCP indicators

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Objective: To establish plan robustness optimization requirements for head and neck cancer (HNC) IMPT cancer treatments.

Methods: The first 10 HNC patients treated with up to 70.00 Gy_{RBE} using IMPT (IBA) on a 6-D robotic couch (Leoni) using a 5-point mask (Orfit) and positioned using daily CBCT. Clinical plans were generated using robust optimization with a $\pm$3% range and 5 mm setup uncertainty (RayStation v6.1). Retrospectively, additional plans were created using a 4, 3, 2- and 1-mm setup uncertainty and a $\pm$3% range uncertainty. Positional accuracy was determined using monthly QA and intra-fractional motion assessment using 41 pre- and post-fraction CBCTs. Range uncertainty magnitude was determined using proton radiography measurements in biological tissue. For each patient and plan, the fractionated treatment course was simulated 25 times by sampling systematic and daily random shifts and systematic range errors. Fraction doses were calculated on weekly verification CTs using different shifts and range errors.

Results: The coverage of both CTVs reduced as a function of the robustness setup shift, resulting in a slightly lower TCP $<$ 0.8% (figure 1). The mean organ at risk (OAR) dose reduced 1.0 Gy_{RBE}/mm robustness setup shift, resulting in 1.9%/mm total normal tissue complication probability (NTCP) improvement (figure 2).

Conclusion: Smaller robustness setup parameters reduces OAR dose and ultimately NTCP, while target coverage and TCP remains acceptable. However, in order to reduce the in-treatment room patient positioning time, a 3mm robustness setup uncertainty was clinically adopted while waiting for data analysis of a larger patient cohort.

PTC58-0401

Evaluation of patient positioning and gaze stability during ocular proton therapy at Italian National Center for Oncological Hadrontherapy (CNAO)

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Purpose: At CNAO ocular proton therapy (OPT) is delivered using a non-dedicated beamline. An optimal gaze direction is established during treatment planning (Eclipse,Varian) and it is reproduced by patient throughout treatment. We report the image-guided evaluation of patient positioning and gaze stability during OPT.

Materials and Methods: Industrial robots are used to accurately position an eye tracking system (ETS) providing a fixation light for gaze stabilization and featuring stereo-cameras for continuous qualitative monitoring the eye motion [1]. Besides, quantitative treatment geometry verification is image-guided by x-ray stereoscopic image acquisition and rigid point-based registration (VerisuitePT,Medcom) of radiopaque clips sutured close to the intra-ocular lesion. Clip positions are compared to the corresponding reference configuration coming from the treatment planning system. A setup correction vector (CV) is computed. If the detected clip positions deviate for more than 0.6mm (along one anatomical direction), beam delivery is stopped and robotic chair position (featuring high mechanical accuracy [2]) is corrected by applying the CV. The ETS continuous monitoring of eye guides the beam on/off and advises the frequency of image acquisition.

CVs of ten patients (P1-P10) were retrospectively collected and 3DCVs are presented.

Results: For each patient and fraction, the distribution of 3DCVs resulting from image pair acquisition is shown (Figure 1). Median(min-max) value of initial 3DCVs over all patients and fractions is 4.4(0.6-8.4)mm (inter-fraction patient-beam alignment/reproducibility). After patient positioning, the 3DCVs overall median(min-max) is 0.5(0-1.3)mm.

Conclusion: Stability of gaze during OPT and adequacy of OPT workflow for correcting setup in case of intra fraction eye motion is assessed. [1] doi:10.1118/1.4915921. [2] doi:10.7785/tcrt.2012.500386.

PTC58-0532

Commissioning and implementation of the automatic gated breath hold technique for pencil beam scanning proton system

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Purpose: To report the commissioning and implementation of the automatic gated breath-hold system using pencil beam scanning (PBS; ProBeam, Varian, USA).

Methods: *Commissioning:* The voluntarily breath-hold spirometry system (SDX, Dyn'R, France) with automatic gating module was commissioned at the Maryland Proton Treatment Center by performing point and 2D-planar dose measurements of 5 gated plans (3-4 fields per plan). For each field, four measurements were performed: three with 2, 3 and 5 breath-hold which were evaluated against the one without breath-hold (reference).

Implementation: The proposed workflow of automatic gated breath-hold treatment and estimated duration time of each step were shown in Figure-1. After instructing the patient how to breathe and hold the breath through the spirometer, the breath-hold level will be set. Next, the CT images will be acquired using SDX breath-hold system as well as normal 4D-CT (as a backup treatment) following by treatment planning on both image sets. At the time of treatment, kV and CBCT images will be acquired at the pre-defined breath-hold level for image guidance. After the patient setup, the treatment will proceed with the automatic gating module active and connected to the ProBeam system.

Results: The maximum percent difference of point dose measurements and the lowest gamma passing rate between non-breath-hold and breath-hold plans were 0.2% and 97.2%, respectively (Table-1). Of 32 patient that were consulted for SDX treatment, 27 underwent SDX simulation and 25 were treated with SDX plan.

Conclusion: The automatic gated breath hold system was successfully commissioned and implemented for PBS proton system.

PTC58-0629

Evaluating dose heterogeneity when using high frequency percussive ventilation as a motion mitigation technique for pencil beam scanning radiotherapy

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Purpose*:* To quantify dose heterogeneity due to the interplay effect when pencil beam scanning protons (PBS) are used with normal-breathing versus high frequency percussive ventilation (HFPV).

Methods*:* HFPV provides frequent mini-bursts of air (100-400/min) into the patient's trachea using a controlled ratio of oxygen inspiration to passive exhalation. We recorded chest wall motion curves using the Anzai laser motion-monitoring system for five (N=5) randomly selected volunteers during both normal-breathing and HFPV. Each chest wall curve was programmed to drive a dynamic CIRS phantom holding high-resolution Gafchromic film. A PBS treatment plan with a known pattern of matchlines was delivered to each film, with and without 4-cm range shifter. We investigated dose heterogeneity, by evaluating film flatness, under normal-breathing, static-film, and HFPV motion conditions.

Results*:* The mean peak-to-peak motion amplitude of normal and HFPV breathing curves were 18.94 mm and 2.11 mm, respectively. Median dose heterogeneity with range shifter was: 24.60% (95% CI: 13.11-39.81%) for normal-breathing, 4.90% (95% CI: 3.27-8.25%) for static-film, and 3.8% (95% CI: 2.89-4.67%) for HFPV. Median dose heterogeneity without range shifter was: 31.30% (95% CI: 25.13-37.75%) for normal-breathing, 7.90% (95% CI: 6.37-8.79%) for static-film, and 5.30% (95% CI: 4.17-6.23%) for HFPV. No difference was noticed from the range shifter, but dose heterogeneity was significantly worse during normal breathing than HFPV.

Conclusion*:* HFPV may address the motion concerns that exist for patients undergoing PBS radiotherapy, by immobilizing the target and decreasing absolute dose heterogeneity by 20-25% when compared to normal breathing. Dose heterogeneity during HFPV was similar to the motionless static-films.

Biology: Mathematical Modelling and Simulation

PTC58-0678

A model for estimation of normal tissue complication probability for proton grid therapy

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Aims: In the present study, we propose a model which can be used for the prediction of normal tissue complication probability (NTCP) in proton grid therapy.

Methods: The proposed model is based on the Lyman-Kutcher-Burman model and categorizes the dose distribution given to a given organ into two distinct dose ranges, either as valley dose (VD) or as peak dose (PD). The $NTCP_{valley}$ and $NTCP_{peak}$ were calculated separately. The NTCP of an organ will then be given by $NTCP = 1-(1-NTCP_{valley})(1-NTCP_{peak})$. To account for the increasing organ tolerance-doses when using smaller beam sizes, a tolerance dose modifying factor, *f*, was introduced for the determination of $NTCP_{peak}$. The proposed model was applied for the estimation of NTCP of the brain, in a Monte Carlo simulation of a brain tumor treatment (Figure 1). A water phantom with a target volume in its center were considered. Grid and uniform beam irradiations were simulated aiming to achieve a similar homogeneity index in the target. The NTCP was calculated for grid irradiations with 1, 2, and 3 mm beam-element widths.

Results: The highest NTCP was determined for the uniform proton-beam irradiation. Intermediate risks were found for the single-grid and the lowest risks were obtained for the interlaced-grid irradiations. Larger beam elements in the grid resulted in larger NTCPs.

Conclusions: Proton grid therapy was found to decrease the NTCP, compared to treatment with uniform beams.

PTC58-0718

Mechanisms of particle relative biological effectiveness (RBE): Effects of DSB clustering on the nanometer scale

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Purpose: To test the hypothesis that pairs of DNA double strand breaks (DSBs) formed within a few nanometers of each other ($\sim$ 1-10 nm) are effectively treated as a single DSB with regards to DSB repair and cell killing.

Methods: The Repair-Misrepair-Fixation (RMF) model links the stochastic distribution of DSB along individual and multiple particle tracks to the distribution of lethal events. In earlier versions of the RMF model, DSB formed along individual tracks were considered independent sites of DSB repair, regardless of the distance between individual DSB. The ion-specific trend towards a decrease in RBE with increasing LET beyond 100-150 keV/mm for ions of $Z>2$ cannot be easily explained by the algorithm used to categorize DSB in the Monte Carlo Damage Simulation (MCDS). We propose a simple probabilistic model to combine closely spaced DSB into a single DSB as a way to test a putative mechanism underlying the trend towards decreasing particle RBE for high LET particles. This hypothesis is tested by comparing various model predictions against measurements for V79, HSG, and T1 cells irradiated by under normoxic and hypoxic conditions by ^{3}He, ^{12}C, and ^{20}Ne ions.

PTC58-0558

Time to think about dose rate in proton beam therapy?

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Recently there has been a resurged interest from the radiotherapy community around ultra-high dose rate (FLASH). However, the biological mechanisms driving this effect remain elusive.

In this work we use our suite of *in silico* models to investigate the potential effects of FLASH on DNA damage and repair for protons. Within the simulation a cell is exposed to a range of clinically relevant doses and LET, delivered at dose rates of 2 Gy/min, 2000 Gy/min, or instantaneously. We take a nanodosimetric approach to predict both the position and time of Double Strand Break (DSB) induction. The DSBs are passed to our models of Non-Homologous End Joining and Homologous Recombination. Within these models DSB ends diffuse through the nucleus whilst progressing along the chosen repair pathway. We score the biological endpoints of misrepaired and residual DSBs as both are thought to be important contributors to radiation induced cell death.

Our result show that dose rate doesn't affect the scored outcomes, Figure 1. Predominantly repair occurs between proximal DSBs created by a single proton track, removing the significance of timing between tracks. We conclude that dose rate, or timing between DSB induction, alone doesn't explain the FLASH effect. A number of, as yet unmodeled, physical and biological mechanisms of FLASH have been proposed in the literature, including chromatin remodelling and oxygen depletion, both of which are areas of further model development.

PTC58-0439

The experimental dose ranges influence the LET dependency of the proton minimum RBE

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Introduction: Models for proton relative biological effectiveness (RBE) are commonly based on two functions, the RBE_{max} and RBE_{min}, describing the extreme RBE at low and high doses. While there is a consensus on increasing RBE_{max} with LET, the LET dependency of RBE_{min} varies between different models. We therefore aimed to analyse this dependency and its sensitivity to variations in the dose range of the cell-survival experiments.

Method and Materials: We analysed published monoenergetic proton cell-survival experiments with $(\alpha/\beta)_x < 5$ Gy and dose-averaged LET (LET_d)$<$20 keV/μm, extracting doses and cell survival data. Restricted databases were generated by sequential exclusion of low dose data from each experiment followed by a linear-quadratic fit to the remaining data. The quadratic component was used to calculate RBE_{min}. The LET_d dependency of RBE_{min} was determined by linear regression of all RBE_{min} values.

Results: Including experiments with doses below 1 Gy resulted in RBE_{min} increasing with LET_d whereas excluding low dose experiments resulted in a constant RBE_{min} (Figure). For LET_d of 5 keV/μm, the RBE_{min} was 1.4 ± 0.1 from a low restriction but reduced to 1.0 ± 0.1 from a high restriction ($>$ 2 Gy) on low doses in the database. None of our restricted databases gave a decreasing RBE_{min} with increasing LET_d.

Conclusion: Our study showed that RBE_{min} has a small yet significant dependency on LET_d for tissues with low $(\alpha/\beta)_x$ ratio. The LET_d dependency of RBE_{min} varied substantially with the experimental dose range. Including experiments with high minimum dose in RBE models may lead to underestimation of the RBE.

PTC58-0349

Analytical modelling of the microdosimetric distributions of mono-energetic proton beams for fast calculations of yD, y* and RBE

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Dose-mean lineal energy (yD) and the saturation-corrected dose-mean lineal energy (y*) are modelled based on microdosimetric distributions $f(\varepsilon_s)$ obtained from Monte Carlo (MC) simulations of the energy deposited per interaction event, ε_s, for mono-energetic proton beams in water with an energy range from 0.6 MeV to 95 MeV. We also performed calculations of Relative Biological Effectiveness (RBE) based on both, MC and the analytical models of y*, using the Microdosimetric Kinetic Model (MKM) for Human Salivary Gland (HSG) cells. Both RBE calculations were then compared to demonstrate the consistency of the agreement between the microdosimetric distributions themselves as well as of any other distributions based on them. Maximun, mininum and average relative differences between MC and analytical values were reported as well as paired Student t-tests to display the goodness of our tool to model, y* and RBE distributions. For values the maximum, minimun and average relative discrepancies were 0.99%, -1.67% and -0.06% respectively. In the case of values these differences were 0.98%, -1.55% and -0.07% specifically, while for RBE values were 0.37%, -0.75% and -0.04% respectively. The Student t-tests showed that no statistically significant differences were observed between MC and analytical values. Our analytical tool has provided instantaneous calculations of the magnitudes of interest, which is in contrast with the computation times required at MC simulations. We have developed an algorithm which provides fast calculations of and y*, with an accuracy close to MC simulations, which could allow to define radiobiological strategies into proton therapy treatment planning

PTC58-0342

Prediction of bladder normal tissue complication probability parameters in spot-scanning carbon ion therapy for prostate cancer

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Purpose: The aim of this study was to predict normal tissue complication probability (NTCP) parameters for bladder after spot- scanning carbon ion radiotherapy (C-ion RT) for prostate cancer.

Methods and Materials: 134 patients were selected to derive NTCP parameters. These patients were treated with relative biological effectiveness (RBE)-weighted dose ranging from 59.2 GyE in 3.7 GyE per fractions to 66 GyE in 2.75GyE per fractions. The Lyman–Kutcher–Burman (LKB) model was used. The deterministic optimization method and the stochastic optimization method were conducted to optimize the maximum likelihood function to determine the values of the LKB model parameters with clinic follow-ups of urinary side effects. The model parameters were fit to the relation between dose and complication observed after C-ion RT.

Results: The resulting NTCP parameters were the volume effect parameter; $n = 0.017$, the steepness of the NTCP curve; $m = 0.094$, the tolerance dose associated with 50% probability of complication; $TD_{50} = 59.2$GyE for Grade ≥ 1 , $n = 0.006$, $m = 0.062$, $TD_{50} = 76.2$GyE for Grade ≥ 2.

Conclusion: A set of bladder NTCP parameters in C-ion RT was determined. The new derived parameter values are helpful for clinicians to optimize radiotherapy plans. However, we consider our results are far from conclusive, and several important issues such as urinary incontinence and pain during voiding need to be further investigated. In future, the prediction will be modified and tested in radiotherapy for prostate in C-ion RT.

PTC58-0355

Dose average LET calculation for proton track segments through microdosimetric Monte Carlo simulations

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Dose average LET can be obtained from Microdosimetric Monte Carlo (MC) simulations. A straightforward uniform sampling of the scoring site turns out to be computationally expensive, whereas for the more efficient weighted sampling approach present some issues. Here we address the issues associated to the latter method and propose adequate corrections to make it available to obtain dose average LET values from microdosimetry. Proton track structures have been simulated with Geant4-DNA considering two different approaches. One employs a uniform sampling by randomly placing the spherical site. The other one uses a weighted sampling by considering the spatial distribution of transfer points. Proposed corrections to the later method make it comparable to the former for LET calculations. An additional MC approach is proposed to obtain the weighted mean of the energy imparted per electronic collision of the proton within the site, the $\delta 2$ function, as an intermediate step in the LET calculation. Energy imparted per event distributions are different when employing both sampling methods, due to the different geometrical randomness. We have found a remarkable agreement for uniform and weighted methods in dose-weighted average LET values when weighted sampling results are corrected according to our considerations. This work shows a reliable and computational-efficient method to perform calculations of track segment dose average LET through MC simulations for proton therapy beams, including the necessary considerations for obtaining the straggling distribution characteristics.

PTC58-0545

An optimizing Monte Carlo code for track and absorbed-dose average LET calculation

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The LET (Linear Energy Transfer) or restricted linear collision stopping power has often been viewed as a key parameter of radiation quality for ion beams in RBE (Relative Biological Effectiveness), which describes the biological effect of charged particles in clinical medical. To obtain a valuable analytical assessment of the radiobiological effectiveness of beams in clinical treatment, a precise average LET based on track or absorbed-dose should be calculated carefully as the clinical beam usually consists of particles with various velocities and charges. Compared to the mono-energetic beam's LET definition and simulation, the most important characteristics of average LET calculation with Monte Carlo codes is the ability to simulate hadronic elastic and inelastic processes and transportation of secondary particles produced in the ions-matter interactions. This paper presents an optimizing Monte Carlo code based on Geant4 to calculate the total track average LET and total absorbed dose average LET including the contribution of secondaries from these interactions with different approaches. To investigate these algorithms dependence, the total average LET results referring to different simulation parameters, such as step lengths, production cuts and physics tables, have also been analyzed respectively. Curves compared to reference stopping power distributions obtained from ICRU49 and ICRU73 show that the proposed approach for total average LET calculation is effective enough to be accepted.

PTC58-0581

Microdosimetric simulations for protons and carbon ions with TOPAS

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Microdosimetric energy depositions have been suggested as a key variable for the modeling of the relative biological effectiveness (RBE) in proton and ion radiation therapy. However, microdosimetry has been underutilized in radiation therapy. Recent advances in detector technology allow the design of new mico- and nano-dosimeters. At the same time, Monte Carlo simulations have become more widely used in radiation therapy. In order to address the growing interest in the field, a microdosimetric extension was developed in TOPAS. The extension provides users with the functionality to simulate microdosimetric spectra, calculate microdosimetric parameters, and determine RBE with a biological weighting function approach or with the microdosimetric kinetic model. The extension was validated using published experimental data for three types of microdosimeters, a spherical tissue equivalent proportional counter (TEPC), a cylindrical TEPC and a solid state microdosimeter. The corresponding microdosimetric spectra and microdosimetric parameters obtained with TOPAS from the plateau region to the distal tail of the Bragg curve generally show good agreement with the experiments.

PTC58-0343

Monte Carlo simulation of microdosimetry and DNA damage based on Geant4 and MCDS toolkit

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Purpose: Understanding of biological effects of radiation is important since new radiotherapy technique have been developed, including proton therapy and flash radiotherapy. Monte Carlo (MC) simulation can simulate DNA damage caused by radiation together with microdosimetry. Here we compared the difference when simulating on cellular scale. *Methods:* Geant4-DNA code, based on track-structure theory, and MCDS software, a fast MC tool based on condensed-history method were adopted. We calculated SSBs and DSBs. A sphere of 10 μm diameter modeled as cell nuclear radiated by mono-energetic protons of 0.5-100 MeV was constructed, and G4EmDNAPhysics_option2 physical process was employed and energy threshold was 11 eV. ClusterAlgo algorithm extended in Geant4 was referred to calculate strand breaks. A total 106 particles were considered for each run. Dose-weighted linear energy spectra for electron were also simulated.

Results: Radio of DSBs and SSBs this study are compared with those in literature in Fig.1. MCDS results were found to yield lower values. The dose-weighted linear energy spectra for electrons with energies below 1 MeV in Fig.2 are almost the same and different from proton and Co-60 extracted from literature.

Conclusion: Preliminary simulation about radiobiological effects of flash using Geant4-DNA and MCDS toolkits was done. Particularly DNA content and oxygen level are considered in MCDS and chemical stage is added in Geant4-DNA package. We will establish a method to represent dose rate considering microdosimetry and DNA damage to explore radiobiological mechanism in MC simulation and validate it by biological experiments in future.

PTC58-0333

A Monte Carlo simulation of DNA double strands breaks owing to secondary electrons

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DNA damage from proton therapy can have three different sources when irradiated, including 1) Direct ionizing radiation such as protons or heavier charged particles. 2) secondary electrons generated by ionization radiation. 3) Free radicals from the interaction between radiation and water. In this study, two Monte Carlo codes for the DSB of electrons with different energies are compared. 1.) DNAPDB with GEANT4 10.04.p02 and G4DNA. This simulator is based on GEANT4 DNA physics and has the model to transport the chemical state, ie the transport of radicals, in DNA damage. 2.) MCDS is a Monte Carlo simulator based on a biological experiment and has the model to simulate the induction and clustering of DNA lesions in normoxic cells. In both simulations, the energy range is set from 10 eV to 1 MeV in 20 bins per decade. In the case of GEANT4, the 1ZBB protein is used as the DNA target. In the MCDS, the target size is set to 3 μm. The result shows that the energy of electrons near 400 eV has the largest DSB probability and the distribution is close to a Gaussian distribution with energy in log scale. In this research, we have established a DSB database for broad electron energies that can be implanted for future simulations to calculate RBE. Also, these data will be using to develop some sensitizer which can induce the secondary electron with kinetic energy close to 400 eV.

PTC58-0148

Magnetic field effects on the microdosimetry and RBE of 330 MeV/u carbon-ion pencil beam

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Purpose: To investigate the effects of magnetic fields on the microdosimetry and relative biological effectiveness (RBE) of 330MeV/u carbon-ion pencil beam.

Methods: Geant4-based Monte Carlo simulations were performed to obtain the dose profiles in a water phantom of carbon-ion pencil beam for situations with longitudinal or transverse magnetic fields with strengths ranging from 0 to 3T. According to the dose profiles, microdosimetric calculations were performed at the corresponding positions for those situations both at the plateau and at the Bragg peak. Then, values of RBE were calculated using the microdosimetric kinetic model for each position in all cases.

Results: Average increases of the RBE values were 0.0%, 0.2% and 1.6% at the plateau, and 0.0%, 0.0% and 0.4% at the Bragg peak for situations with longitudinal magnetic fields of 0.5, 1.0 and 3.0T, respectively. However, for the scenarios with transverse magnetic fields, a lateral asymmetry of RBE values was observed at the positions in both the plateau and Bragg peak regions. A maximum variation around $\pm$3% for RBE values was found at the Bragg peak with 3T transverse magnetic field.

Conclusions: Both longitudinal and transverse magnetic fields affect the microdosimetry and RBE of carbon-ion pencil beam. RBE fluctuations of less than 1% can be reached under longitudinal magnetic fields below 1T and under transverse magnetic fields below 0.5T for carbon-ion pencil beam. Necessary corrections of RBE should be implemented for situations with magnetic fields beyond these thresholds.

Biology: Drug and Immunotherapy Combinations Poster Discussion Sessions

PTC58-0406

The effects of Niraparib, a PARP-1/-2 inhibitor, in sensitizing human head and neck cancer cells to proton and photon radiation

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Purpose: Radiotherapy (photon [XRT], proton [PRT]) in combination with targeted therapy is a promising less toxic strategy for patients with head and neck cancer (HNSCC). Niraparib is an orally bioavailable poly-(ADP-ribose) polymerase (PARP)-1 and PARP-2 inhibitor, which targets DNA damage repair (DDR). Whether niraparib can influence the response of HNSCC cells to XRT or PRT and the impact of niraparib on the relative biological effectiveness (RBE) of PRT versus XRT are unknown. We investigated these unknowns in human HNSCC cell lines of differing human papillomavirus (HPV) status.

Methods: Cell lines HN5, SqCC/Y1 (HPV-), and UMSCC-47, UPCI-SCC-154, UPCI-SCC-152 (HPV+) were used. Cellular colony forming (assessed by plating efficiency), radiosensitivity (assessed by clonogenic cell survival) and radiation-induced DNA double-strand breaks (DSBs, assessed by 53BP1 foci) were determined. Niraparib (1 μM) was given 1 hour before irradiation.

Results: Niraparib reduced colony formation in HN5 (85.7% relative to untreated) and UPCI-SCC-154 (69.3% relative to untreated) cells. Niraparib enhanced the radiosensitivity of all 4 cell lines at 0.1 cell survival fraction; Niraparib induced improved RBEs of PRT versus XRT were also observed (Figure 1). Niraparib prolonged the presence of DSBs at 24h after XRT or PRT in these cells (Figure 2).

Conclusion: Niraparib enhanced radiosensitivity of 4 HNSCC cell lines to both PRT and XRT, with improved RBEs by a possible mechanism of Niraparib inhibited DDR. These data suggest that Niraparib may have potential to improve the efficacy of both PRT and XRT in patients with HNSCC. Further *in vivo* and mechanistic studies are warranted.

PTC58-0163

Combination therapy using a dopamine receptor D1 agonist and carbon ion beam inhibit mammary tumor growth and bone metastatic potentials

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Dopaminergic signaling plays a critical role in the nervous system, but little is known about its potential role in breast cancer and bone metabolism. A screening of ∼ 1, 000 biologically active compounds revealed that a selective agonist of dopamine receptor D1 (DRD1), A77636, inhibited proliferation of 4T1.2 mammary tumor cells as well as MDA-MB-231 breast cancer cells. Herein, we examined the effect of A77636 on bone quality using a mouse model of bone metastasis from mammary tumor. A77636 inhibited migration of cancer cells in a DRD1-dependent fashion and suppressed development of bone resorbing osteoclasts by downregulating NFATc1 through the elevation of phosphorylation of eIF2α. In the mouse model of bone metastasis, A77636 reduced osteolytic lesions and prevented mechanical weakening of the femur and tibia. Next, we examined the effect of combination therapy using A77636 and carbon ion beam on tumor growth and bone quality. Combination therapy enhanced the tumor cell killing and reduced osteolytic lesions compared to alone DRD1 agonist. Collectively, we expect that dopaminergic signaling might provide a novel therapeutic target for breast cancer and bone metastasis in particle therapy.

PTC58-0133

Development of a magnetic nano-graphene oxide carrier for improved glioma-targeted drug delivery and imaging: In vitro and in vivo evaluations

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To overcome the obstacles inflicted by the BBB in Glioblastoma multiforme (GBM) we investigated the use of Multifunctional nanoparticles that designed with a Nano-graphene oxide (NGO) sheetfunctionalized with magnetic poly (lactic-co-glycolic acid) (PLGA) and was used for encapsulation and glioma targeting delivery of radiosensitizing drug 5-iodo-2-deoxyuridine (IUdR). The in vitrobiocompatibility of the nanocomposite has been studied by the MTT assay. In vivo effect of magnetic targeting on the extent and selectivity of nanoparticle accumulation in glioma-bearing rats under an external magnetic field (MF) density of 0.5 T was easily monitored with MRI. IUdR-loaded magnetic NGO/PLGA with a diameter of 71.8 nm, a zeta potential of -33.07±0.07 mV, and a drug loading content of 3.04±0.46% presented superior superparamagnetic properties with a saturation magnetization (Ms) of 15.98emu/g. Furthermore, Prussian blue staining showed effective magnetic targeting. The tumor volume of rats after treatment with IUDR/NGO/SPION/PLGA+MF was decreased significantly compared to the rats treated with saline, IUdR and SPION/IUdR/NGO/PLGA.In conclusion, we developed magneticIUDR/NGO/PLGA, which not only achieved to high accumulation at the targeted tumor site by magnetic targeting but also exhibited significantly improved therapeutic efficacy and toxicity for glioma both in vitro and in vivo. This innovation increases the possibility of improving clinical therapeutic efficiency of chemotherapeutic agents, or lowering the total drug dose to reduce systemic toxicity.

Biology: Enhanced Biology in Treatment Planning Poster Discussion Sessions
PTC58-0399

Quantification of dose calculation uncertainties in proton beam therapy for head and neck patients using GPU-accelerated Monte Carlo code FRED

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Monte Carlo (MC) simulations are essential for accurate dose calculation in proton beam therapy (PBT). The treatment planning system (TPS) exploits analytical algorithms assuming constant radiobiological effect (RBE=1.1). The limitations of the TPS dose estimations can lead to inaccurate calculations of biological dose deposited in the patient.

The GPU-accelerated MC code FRED combines the high dose calculation accuracy with computational performance and offers different RBE models for biological dose calculation (constant RBE, biophysical and phenomenological models). FRED was experimentally validated in the Krakow PBT center in homogeneous and heterogeneous media (Rucinski et al. submitted to MP), showing better agreement with respect to the TPS. Based on treatment plans of 10 head and neck (H&N) patients treated in Krakow, we compare FRED and TPS calculations to systematically quantify physical and biological dose calculation uncertainties. The dose delivered to the planning target volume (PTV) and organs at risk (OARs) as well as the clinical volumetric indices were evaluated.

The commissioning of FRED and quantification of the clinical dose calculation uncertainty for patients will be presented (Tab.1). In the example of a H&N patient (no.1) in Fig.1, the mean dose (RBE=1.1) in PTV was 54.00 and 55.27 Gy(RBE), whereas maximum dose delivered to the brain stem was 55.23 and 53.15 Gy(RBE) for FRED and TPS, respectively.

The quantification of biological dose uncertainties in PBT using FRED code and RBE models can eventually improve the quality of PBT treatments.

PTC58-0587

Assessment of the skin reaction of head and neck cancer based on the variable radiation biology model

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Purpose: Skin reaction for head and neck patients is commonly observed in proton therapy. In this study, we aimed to evaluate the dose variations of tumor, skin between the constant and variable relative biological effectiveness (RBE) models and understand the skin reaction in the context of enhanced RBE effects in the skin region.

Materials and Methods: Two oropharynx cases treated with intensity-modulated proton therapy (IMPT) was retrospectively reviewed. The treatment plans created by Eclipse were re-calculated by an in-house developed Monte Carlo-based algorithm and four variable RBE models (Repair-Misrepair-Fixation, Wedenberg, McNamara, Wilkens and Oelfke) were employed. Skin within the 3 cm expansion of clinical target volume (CTV) was selected for analysis. Dose variations was assessed by comparing dosimetric indices between constant and variable RBE dose.

Results: Comparing to constant RBE of 1.1, variable RBE models predict averaged dose variations of 1.9%, 0.3% and 5.3% in mean CTV dose, CTVD98 and CTVD2 respectively, whereas the dose variations in skin could be as high as 23.8% and 25.3% for mean dose and D2. The D2 of skin ranges from 64.8 Gy to 78.9 Gy compared to 60.0 Gy assuming constant RBE of 1.1.

Conclusions: The difference between constant and variable RBE dose in tumor region is small. However, skin adjacent to the tumor was likely to fall into the distal edge of the proton beams and may receive a substantial higher dose using variable RBE model. Larger skin reaction may be correlated with the significantly enhanced RBE arisen from increased LET.

PTC58-0435

New Hybrid 3D analytical linear energy transfer (LET) calculation algorithm based on the pre-calculated data from Monte Carlo (MC) simulations

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Purpose: To develop an analytical, fast LET calculation code for biological effects evaluation and LET-guided robust optimization in spot-scanned proton therapy (SSPT).

Methods: The method is analogous to the pencil beam algorithm to calculate the dose in proton therapy with the 3D LET calculation kernel generated by MC as follows: *Step-1*: Using a well-benchmarked MC code to generate LET distributions of single energy proton beams in water for all energies and derive the dose-averaged LET (LET_d) lateral profiles at various depths. *Step-2*: Using a customized ‘‘error function’’ to fit the aforementioned LET_d lateral profiles (*Fig.1*), and store the fitted coefficients as a lookup table. *Step-3*: During the dose/LET calculation, the stored fitted coefficients and the fitting function will be used to calculate the LET_d values based on the spot energies and the water equivalence thickness in both beam and lateral directions. We then validated the improvement of our new method by comparing the calculated LET distributions with MC simulation and the previous 1D analytical LET model in twelve patients with different disease sites.

Results: Compared with MC, our new method only under-estimates LET_d values by ~5% in the penumbra region, while the previous 1D model under-estimates it by ~36% *(Fig.2)*. Typical calculation time on an inexpensive workstation was two minutes.

Conclusion: Our 3D analytical method can, (1). calculate LET_d in SSPT accurately and efficiently, (2). improve the OAR protection by reducing the hot LET spots in OARs based-on the LET-guided optimization, (3). easily to be used by other analytical codes.

PTC58-0489

Radiobiological effectiveness difference of proton arc beams versus conventional proton and photon beams

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To demonstrate the larger biological effectiveness of PMAT compared to IMPT or conventional therapy (6MV photons) for cells of different radiosensitivity exposed under the same experimental conditions with each modality. Cells were cultured in Petri dishes placed in the central axis of a cylindrical solid water phantom of 20cm in diameter. For the PMAT plan, cells were exposed to 13 mono-energetic proton beams separated every 15deg over a 180deg arc, with each field designed to deliver uniform dose and higher LET to the Petri dishes. For the IMPT plans, 3 fields were used, where each field's Bragg peak was spread to cover the full target. For the photon plan, a single IMRT plan was used to create a uniform dose across the target. A clonogenic assay was performed in order to measure the relative biological effectiveness of the PMAT plans compared with the IMPT and the IMRT plans. Similarly, in order to study the quantity and quality of the DNA damage induced by the PMAT plans compared to that of the IMPT or IMRT, g-H2AX assays were conducted to study the relative number of DNA damage induced by each modality and their repair rate with time. The hypothesis behind the enhanced effectiveness of PMAT is the increased DNA damage induced by the higher values of Linear Energy Transfer (LET) observed in PMAT compared to IMPT. This is demonstrated by the lower cell survival and higher proportion of unresolved DNA damage respectively shown after PMAT compared to the other modalities.

Biology: BNCT Poster Discussion Sessions
PTC58-0586

Application of dynamic infrared imaging to BNCT studies

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As part of the Boron Neutron Capture Therapy (BNCT) project conducted by the Argentine National Atomic Energy Commission (CNEA), Dynamic Infrared Imaging (DIRI) has been included in different research and clinical protocols. DIRI is based on the detection of the infrared radiance emitted by the area under evaluation, acquired non-invasively by high sensitivity infrared thermal cameras. It describes real-time temperature distributions during transient evolution, giving information that is a consequence of the internal distribution of heat sources, like inflammation or metabolism, material composition and surface properties, like moisture. This technique is currently implemented in our group in different BNCT research projects, such as: To assess the characteristics of tumors, precancerous and normal tissues and radiation-related mucositis in the hamster cheek pouch oral cancer model and radiation-related dermatitis in the rat colon cancer model; To understand the effects of tissue temperature rising during the electroporation protocol in the hamster cheek pouch oral cancer model; To analyze the evaporation process in histological sections for neutron autoradiography; To monitor the temperature evolution during explanted organ cooling in a preclinical protocol to study ex-situ BNCT irradiation in sheep lungs; Patient characterization pre-treatment and follow-up post-BNCT. DIRI proved valuable to obtain information in real time, without interfering with the observed specimen or process. In particular, ongoing DIRI studies will be aimed at exploring temperature heterogeneities that would otherwise go unnoticed and contribute valuable diagnostic and prognostic data, taking advantage of its ability to describe fast and time-dependent heat transfer processes that could affect the results.

PTC58-0341

The biological effect of boron neutron capture reaction dose can be predicted by nucleo-cytoplasmic ratio or cell size

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The relationship between the BNCT tumor dose and the effect is not always clear. The uncertainty of estimation of tumor ^{10}B concentration, the variation of radiation sensitivity of tumor cells and the complexity of an interaction among four types of radiation consisting of BNCT dose may be considered as the reasons. We reanalyzed the data of our previous papers to investigate the variation of radio-sensitivity of tumor cells to $^{10}B(n,alpha)^{7}Li$ dose: the dose generated by the reaction of thermal neutron and ^{10}B, thereafter boron-neutron dose. The radio-sensitivities of 5 tumors of EL4, SAS/neo, SAS/mp53, SCCVII and B16-BL6 melanoma were examined. In the combination of *p*-Boron-L-phenylalanine (BPA:$C_9H_{12}BNO_4$) with neutron beam, D_0 of cell survival curve to the boron-neutron dose was the smallest for SAS/neo and followed by EL4, SAS/mp53, SCCVII, B16-BL6 melanoma in order. In the combined use of mercaptoundecahydrododecaborate (BSH: $Na_2B_{12}H_{11}SH$) with neutron irradiation, D_0 for EL4 was the smallest, SAS/neo, B16-BL6 melanoma, SAS/mp53 and SCCVII were in that order. The relationships between these D_0 values and nucleo-cytoplasmic ratios (Xnc) or cell size index (Xcs) obtained by histopathological microslide image were as follow: ($D_0 = 0.1341Xnc^{-1.586}$, $R^2 = 0.9721$) for all tumors in BPA-BNCT and $D_0 = 0.0122Xcs - 0.1319$ ($R^2 = 0.9795$) for 4 tumors except B16-BL6 melanoma in BSH-BNCT. Based on these results, we have proposed a new biologically equivalent effectiveness factor: absolute biologic effectiveness (ABE) factor. ABE factor is Gy/D_0. Then ABE dose is physical dose x ABE factor and it means the dose to decrease the cell survival rate to $e^{-ABE\ dose/Gy}$.

PTC58-0088

A proposal towards an international standard for reporting BNCT

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For decades the clinical use of BNCT was limited due to the need for reactor-based neutron sources, which were often located at unacceptable distances from the hospital. Recently, hospital-based accelerators have become available leading to a renaissance of this modality.

In order to compare and to repeat results, an internationally accepted reporting system is long overdue. Numerous models for prescribing the irradiation dose have been developed and successfully used but only on a quasi-national level. Efforts to develop an international standard for reporting dose in BNCT, such as the IAEA TECDOC 1223, have been made but its global implementation was not successful.

The absorbed dose is the basic parameter for prescribing, recording and reporting in radiotherapy. However, in BNCT, non-stochastic "single hit effects" have to be taken into account so that the absorbed dose concept is not suitable to predict, and report expected biological or clinical effects. Furthermore, in BNCT, other dose components with different biological effects have to be considered.

We demonstrate that Φ (the thermal neutron fluence integrated over the irradiation time) together with the concentration of ^{10}B in blood are the most important parameters for reporting. If these parameters are reported, together with the quantity of fast neutrons and gamma rays emitted by the source, they can be used as input parameters for any treatment planning system, thereby obtaining a good estimation for understanding and reproducing results observed elsewhere. We hope that our suggestion will contribute to the discussion for developing an international standard for reporting BNCT.

PTC58-0081

Evaluation of neutron fluence measurement system utilizing a LiCAF scintillator - optical fiber detector for BNCT

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Introduction: In boron neutron capture therapy (BNCT), the gold radio-activation is the primary method for measuring neutron fluence and flux. This method, however, is offline and time consuming. To simplify neutron measurements, online/real-time systems utilizing a scintillator detector have been actively researched. In this study, we evaluated our online neutron fluence measurement system (NeuFluenT) utilizing the accelerator-based BNCT system installed at Osaka medical college.

Materials and Methods: In order to evaluate the measurement accuracy of the system, we measured and compared the central-axis depth flux in a 20×20×20 cm water phantom with the depth curve obtained via the gold radio-activation method. We also evaluated the count linearity, interference due to simultaneous use of multiple detectors, and discrimination of neutrons from gamma rays using a ^{6}LiF filter. As a neutron source, we utilized a 30 MeV cyclotron-based epithermal neutron source (C-BENS) manufactured by Sumitomo Heavy Industries, Ltd.

Results: The in-phantom neutron flux distribution obtained by our system was equivalent to that obtained by the gold activation method. Our system showed good linearity and no sign of influence on measurement results when three detectors were placed next to each other. Discrimination of neutrons from gamma rays was also good.

Conclusion: Our evaluations indicated that neutron flux measured with NeuFluenT was consistent with the gold activation method. Because simple and accurate measurements are possible with this system, we expect that it will significantly reduce the time necessary for periodic beam quality checks.

PTC58-0391

Feasibility of Newly constructed LINAC based BNCT for malignant melanomas

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We constructed a newly designed LINAC based BNCT treatment facility. It succeeded to make beam of 1.4-2.0mA current and continuous operation more than 90min. Measurement data with a water phantom revealed that the thermal neutron flux was 8.13×10^{8} n/cm^{2}s and the maximum gamma dose rate was 2.4Gy/hr. at the depth of 2cm. Fig.1 showed the experimental data (circle) and Monte-Carlo simulation data (triangle) of the central beam axis dose distribution. Epithermal neutron ($0.5<E<10$keV) flux (diamond), and fast neutron ($10\text{keV}>E$) flux (square) data were normalized to the 1.4mA operation.

Malignant Melanoma was a target disease in an early phase of development BNCT. To planning clinical trial for the patients of malignant melanomas, we analyzed the feasibility using Monte-Carlo simulation code and these neutron flux profiles.

This study considered use of 500mg/kg of boronophenylalanine, the tumor boron concentration was assumed 84mg/mL. the lesion covered with 2-cm bolus and maximum normal skin dose is limited to 15Gy-Eq. Fig.2 showed the result of simulation. Maximum tumor dose would be 54.3Gy-Eq. The tumor dose of 6cm depth is 12.2 Gy-Eq. (The deepest lesion of eligibility criteria in our protocol has been 6cm.) The BNCT total dose are composed boron dose, Hydrogen dose, Nitrogen dose, and Gamma-ray. From these results, initial response can be expected in clinical research by more than 50Gy-E dose at the 1cm depth. Neutron radiation time would be 45min with 1.4mA operation, that are tolerable treatment time and make it shorter that would more high current.

PTC58-0384

Folate-modified cyclodextrin improved the active tumor accumulation and therapeutic effect of BNCT using BSH

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The therapeutic effect of boron neutron capture therapy (BNCT) greatly depends on the boron accumulation into the tumor, but the accumulation of existing compounds is limited. In this study, folic acid-modified cyclodextrin (ND201) purified with folate receptor (FR) was used to examine the improvement of specific and active accumulation of boron compounds on tumors. Colon-26 (FR+) and A549 (FR-) cells were inoculated to the behind of right legs of mice. The BSH mixed with ND201 was subcutaneously injected to the back of the neck of the mice. Boron concentration in the tumor cells was measured with ICPS-8100 (Shimadzu Corporation). The stability constant (Kc) and the stoichiometric ratio of BSH/ND201 complex (ND-BSH) were 1.4×10^4 (/M) and 0.5, respectively. It was found that ND-BSH stably binds in the blood, and the mixing ratio of 1: 1 is most efficient. ND-BSH showed high boron concentration (38.5 ppm) compared with BSH alone (11.25 ppm) for Colon-26 (FR+) tumors. The maximum tumor/blood ratio (T/B ratio) by ND-BSH was too high (6.58) compared with BSH alone (1.04) for Colon-26 (FR+) tumors. On the other hands, T/B ratio was similar between ND-BSH and BSH for A549 (FR-) tumors. After neutron irradiation, ND-BSH showed significant tumor suppressing effect compared with BSH alone (only for Colon-26 tumor). It was suggested that the usefulness of BSH-ND201 depends on the expression of folate receptor and chemical modification targeting folate receptor to existing boron compounds may contribute to improvement of therapeutic effect of BNCT.

PTC58-0073

Evaluation of BNTC + oligo-fucoidan in an ectopic colon cancer model

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Introduction: BNCT combines selective tumor uptake of ^{10}B compounds and neutron irradiation. The ectopic model of colon cancer in BDIX rats is used by our group for BNCT studies. This model allows for the evaluation of local tumor response, radiotoxic effects, abscopal effect and incidence of metastasis in proximal ganglia. Oligo-Fucoidan has anti-inflammatory and anticancer activities. The aim of the present study was to evaluate the therapeutic efficacy of BPA-BNCT combined with Oligo-Fucoidan.

Materials and Methods: An initial study involved a group of 6 BDIX rats bearing tumors in the right hind flank. BDIX rats were injected subcutaneously in the right hind flank with DHD/K12/TRb syngeneic colon cancer cells. Three weeks later, the tumor-bearing legs were treated locally with BPA-BNCT at RA-3 Nuclear Reactor and Oligo-Fucoidan (200mg/ml) was administered orally, once a day, starting the day prior to irradiation and continuing for 14 days after BNCT (total 16 days).

Results and Conclusions: Oligo-Fucoidan was not toxic. Although it did not reduce the incidence of severe dermatitis, it did significantly enhance therapeutic effect expressed as a reduction in the mean ratio of tumor volume post BNCT/Pre BNCT: BNCT+Oligo-fucoidan 0.35 vs BNCT only 1.09. Ongoing studies are aimed at testing different Oligo-Fucoidan administration protocols, exploring the potential effect of Oligo-Fucoidan on boron targeting and assessing the influence of Oligo-Fucoidan on the local and abscopal effect of BNCT+immunotherapy.

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PTC58-0092

Boron microdistribution at cellular and tissue level through neutron autoradiography

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When considering a BNCT protocol, the knowledge of the spatial localization of boron atoms is essential, as the BNC products, alpha and lithium produce a lethal damage in a short path. There are few techniques that provide this information, being the neutron autoradiography especially suitable due to high resolution and low cost.

Neutron autoradiographies can be generated by putting in contact a boron-loaded biological matrix (cell cultures, tissue section) with a polymeric nuclear track detector (NTD). By irradiating this assembly with thermal neutrons, the BNC reaction takes place and the alpha and lithium particles impact on the NTD. By performing a chemical process, this latent damage can be enlarged up to optical level. The boron spatial distribution can be assessed by mapping the etch pits on the NTD.

We have set-up different approaches of neutron autoradiography: (1) qualitative autoradiography (QLA),that implies irradiation with high neutron fluencies and longer etching times, allowing the observation of boron microdistribution through differences in shades of grey (e.g. Fig 1); (2) quantitative autoradiography (QTA), that converts track density (number of tracks per unit area) measurements into absolute boron concentration values using a calibration curve; and (3) UV-C sensitization of polycarbonate (UVC-A) that produces an imprint of the biological material on the NTD, thus enhancing spatial resolution (e.g. Fig 2). We have applied them to different cell lines and biological in vivo models. In this work we will present the last updated data of these approaches.

PTC58-0107

Boron biodistribution study for bnct with boric acid and boronophenylalanine in an oral cancer model

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Introduction: A critical aspect of the therapeutic efficacy of BNCT is the biodistribution of ^{10}B in tumor and in the dose limiting normal and precancerous tissues in the target volume. The aim of this work was to perform boron biodistribution studies with Boric Acid (BA) + Boronophenylalanine (BPA) administered jointly in the Hamster Cheek Pouch Oral Cancer Model (HCPOCM) to optimize the homogeneous boron uptake in heterogeneous tumors thus increasing tumor response to BNCT *in vivo*.

Materials and Methods: Syrian hamsters bearing exophytic tumors (Squamous Cell Carcinoma) induced by cancerization with Dimethylbenzanthracene (DMBA) were used. Five AB+BPA administration protocols with different final doses of B (66 mg^{10}B/Kg, 50 mg^{10}B/Kg and 36 mg^{10}B/Kg) and different proportions of each of the compounds were evaluated. Tissue samples were processed for measurement of absolute gross boron concentration ([B]) by ICP-OES and B microdistribution by Neutron Autoradiography (NA).

Results: The [B] for the protocols tested was: 80, 60 and 40 ppm (tumor); 55, 55 and 33 ppm (precancerous tissue); 55, 50 and 33 ppm (normal tissue), considering the 3 final B concentrations of 66, 50 and 36 mg^{10}B/Kg respectively. For all protocols, preferential tumor uptake was observed versus precancerous tissue (T/Pr), normal tissue (T/NT) and blood (T/B) with values ranging between 1.1 and 3.2.

Conclusion: Dosimetric calculations indicate that the absolute values of B in tumor would be therapeutically useful and ongoing studies of in vivo BNCT mediated by BA+BPA will provide information on therapeutic efficacy and radiotoxicity in the HCPOCM.

PTC58-0602

Evaluation of novel boron compound for boron neutron capture therapy using rat brain tumor model

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Introduction: Boron neutron capture therapy (BNCT) is form of tumor-cell selective particle irradiation using low energy neutron irradiation of non-radioactive boron-10 (^{10}B) to produce high energy alpha particles (^{10}B [n, alpha] ^{7}Li). To develop practical materials utilizing ^{10}B carriers, we designed and synthesized novel boron drug (AAL) which is the compound containing many boron-10 atoms like BSH, utilizing the amino acid demand enhanced by tumor like BPA, and combines the characteristics of both.

Materials and Methods: We evaluated the boron concentration of F98 glioma cells for ^{10}B compounds, BPA, and AAL in vitro, and the biodistribution of these following BPA administrated intravenously (i.v.) or AAL administrated by convection-enhanced delivery (CED) in F98 glioma bearing rats. For *in vivo*, F98 glioma bearing rats were divided to six groups.

Results: *In vitro*, AAL attained higher cellular uptake F98 glioma cells compared with BSH, but less than BPA. *In vivo* biodistribution study, the AAL(CED) 6h after termination group attained highest boron concentrations of tumor (59.9 $\pm$ 18.2 μg/g). The corresponding ipsilateral normal brain concentrations were low (2.9 $\pm$ 0.5 μg/g). Median survival times (MST) of untreated and irradiated controls were 26.5 (25–28) and 28 (26–30) days, respectively, while rats that received AAL(CED), followed by BNCT, had a MST of 31 (29–35) days, which were shorter than those obtained following i.v. administration of BPA (34 (33–36) days). And the combination group had an MST of 38 (36–40) days.

Conclusion: This study suggested the possibility that AAL became the drug to add curative effect for BNCT.

PTC58-0084

BNCT mediated by BPA + Oligo-Fucoidan for the treatment of oral cancer in the hamster cheek pouch experimental model

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Introduction: Unresectable head and neck tumors are treated with radiation therapy or chemoradiotherapy, but the dose that can be administered to tumor is limited by toxicity in precancerous tissue. Oral mucositis is a frequent, dose-limiting side effect which represents an important unmet medical need in oncology. BNCT (Boron Neutron Capture Therapy) combines selective tumor uptake of 10-B compounds and neutron irradiation. We previously demonstrated the therapeutic effect of BNCT in the hamster cheek pouch oral cancer model and studied the dose-limiting radiotoxic effects (mucositis) of BNCT. Oligo-Fucoidan is extracted from seaweeds and has exhibited anticancer and anti-inflammatory properties. Herein, we evaluated if Oligo-fucoidan was able to reduce radiotoxicity (mucositis) induced by BNCT mediated by BPA (boronopheylalanine) in the Oral cancer & Precancer model in the hamster cheek pouch.

Materials and Methods: Cancerized hamster cheek pouches (8-week protocol) were exposed to BPA/BNCT at 3Gy and 2Gy to precancerous tissue with or without Oligo-Fucoidan. In another group of cancerized hamsters, we performed boron biodistribution and autoradiography studies to evaluate if Oligo-fucoidan affects boron biodistribution.

Results and Conclusion: Oligo-fucoidan did not reduce severe mucositis. However, Oligo-fucoidan+BNCT at 3Gy increased tumor overall response vs BNCT: 94% vs 67%. Oligo-fucoidan+BNCT 2Gy is currently under evaluation, to assess if Oligo-Fucoidan allows for a reduction in BNCT dose to decrease mucositis without affecting BNCT therapeutic efficacy. The effect of Oligo-Fucoidan on boron biodistribution and microdistribution is under evaluation.

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Biology: Translational and Biomarkers Poster Discussion Sessions
PTC58-0346

High-dimensional single-cell analysis reveals the immune response of carbon ion radiotherapy

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Radiotherapy can change the distribution of some immune cell subsets and immune cell functional state in tumor microenvironment, and further affect the tumor immune state of the body. Although carbon ion radiotherapy (CIRT) has a high local tumor control rate, in most cases, radiotherapy must be combined with systemic therapy to control metastasis and increase survival. Therefore, it is necessary to systematically study the immune effects of heavy ion radiotherapy. Here we used high-dimensional single-cell mass cytometry in combination with algorithm-guided data analysis for the in-depth characterization of the immune cell subsets in the peripheral blood of prostate cancer (PCa) patients before and after CIRT. The results showed that the proportion of CD4+ regulatory T cells (CD4+CD25+CD127-FoxP3+) decreased significantly after CIRT compared with before CIRT ($p < 0.05$). And it was found that CD4+ T effector cells had a higher proportion in patients with good response of CIRT. Additionally, it was found that a large number of cytokines of B cells were involved in immune regulation. This study demonstrated for the first time the subgroup marker spectra of T and B cells in PCa patients before and after CIRT, providing an important reference for combined immunotherapy with CIRT. In this study, it was found that immune cell subsets analysis may serve in clinical decision support of CIRT. This work was supported by the National Key R&D Program of China (2017YFC0107600) and the National Natural Science Foundation of China (81773225).

PTC58-0697

Response of human hematopoietic stem and progenitor cells to neutron radiation: Impact on leukemia risks after pediatric proton therapy

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The high leukemia risk after childhood radiation exposure is related to the high sensitivity of the red bone marrow at young ages, harboring the hematopoietic stem and progenitor cells (HSPC). While proton therapy is of great interest for the treatment of pediatric brain tumors due to the optimal dose distribution, some degree of normal tissue injury is inevitable and serious concerns remain regarding secondary neutrons produced in proton therapy. Since 27.8-17.5% of the red bone marrow is located in the head of children in the first five years of age, it is important to estimate the sensitivity of HSPC to low neutron doses.

HSPC isolated from umbilical cord blood were enriched for CD34 and irradiated with ^{60}Co γ-rays and p(66)+Be(40) neutrons at iThemba LABS (average energy 29 MeV; average LET 20 keV/μm). Apoptotic cell death, DNA double-strand break (DSB) repair and chromosomal aberrations were determined.

As expected, an increase in apoptosis and chromosomal aberrations were observed, both effects being more pronounced for neutrons compared to γ-rays. Interestingly, the number of radiation-induced DNA DSB was initially lower after neutron irradiation compared to the direct damage measured after irradiation with ^{60}Co γ-rays, but similar levels were observed 24h after irradiation.

Despite the fact that HSPC are considered to be radiosensitive, relative biological effectiveness (RBE) values of neutrons are high. The findings obtained in this study shed new light on the response of HSPC to neutron radiation, which are important to predict the risk on leukemogenesis or radiation-induced myelosuppression in pediatric proton therapy.

PTC58-0221

MRI-based radiomics in carbon-ion therapy of skull-base chordomas: Preliminary results for predicting local control

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Purpose: To evaluate the feasibility of using MRI to predict local control (LC) in skull-base chordoma patients treated with carbon-ion radiotherapy (CIRT).

Materials and Methods: From 2014 to 2016, 56 retrospectively selected patients affected by skull-base chordoma underwent CIRT (70.4 Gy (RBE), 16 fractions) at CNAO (Pavia, Italy). Prior to treatment, T1-weighted (range: TE/TR=2.48-11/377-887 ms, flip-angle=67-150°, resolution=0.47x0.47x3-0.97x0.97x3 mm) and T2-weighted (range: TE/TR=76-104/2400-10951 ms, flip-angle=80-150°, resolution=0.46x0.46x3-0.78x0.78x5 mm) 2D contrast-free MR images were acquired. Planning CTs were rigidly registered to MR images to convey tumor contours. LC, defined as a progression-free disease at follow-up (median follow-up time: 34.5 months, overall LC=68%), was the endpoint. After bias field correction and intensity normalization (Fig.1), 107 2D radiomic features (14 shape, 18 first order, 75 texture) were extracted from each T1w- and T2w-MRI. Supervised feature selection was applied before training a random forest classifier. The area under the curve (AUC) of the ROC curve was computed both for training (mean±standard deviation, over 10-fold cross-validation) and testing (20% hold-out of the dataset).

Results: Training and test AUC were respectively 0.644±0.31 and 0.688 for T1w-MRI, whereas lower AUCs (0.628±0.31 and 0.641) were found for T2w-MRI. When combining T1w- and T2w-derived features, the AUC reached 0.684±0.30 in training and 0.781 on test data (Fig.2).

Conclusions: MRI-based radiomic features were used to predict LC in skull-base chordomas treated with CIRT for the first time. The combination of T1w and T2w-derived features improved the classifier predictive power, but deeper investigations on pre-processing and feature selection methods could further improve the results.

PTC58-0610

Non-invasive plasma metabolomic profiling reveals carbon ion radiotherapy efficacy in prostate cancer

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Background: Prostate cancer's (PCa) incidence and mortality rates are rising both in developed and developing countries. Carbon ion radiotherapy (CIRT) is an effective precision treatment for PCa. However, litter research was reported to predict efficacy of carbon ion therapy in the clinic. Metabolomics-based methods present biological phenotypes at the metabolite level and validating potential biomarkers, which holds a great potential for precision treatment.

Methods: In this study, plasma samples were harvested from patients(n=52) with localized prostate cancer before and after CIRT. These samples were detected with NMR-based metabolomic approach. Univariate and multivariate statistical analyses were required. the characteristic of patient was provided in table. ROC curve was used to discriminate the good response patients from the poor response group.

Results: Results showed that 31 plasma metabolites were identified in localized PCa patients involving several key metabolic pathways such as Amino acid metabolism, Central carbon metabolism in cancer, TCA cycle, Biosynthesis of other secondary metabolites. Differentially expressed metabolites, such as Tyrosine, Lactate, Alanine, Valine, and leucine, are of great statistical significance, which warrants further validation as potential biomarkers for PCa (combined with differential metabolites AUC=0.749). What's more, high expression of Tyrosine, Lactate, Alanine, Valine, leucine after CIRT is associated with immediate efficacy (PSA<0.2ng/ml).

Conclusion: Therefore, we propose that metabolomic profiling approach is a promising screening tool for predicting the efficacy of carbon ion therapy of PCa patients. This work was supported by the National Key R&D Program of China (2017YFC0107600), and the National Natural Science Foundation of China (81773225).

PTC58-0618

Relationship between microcephaly and learning disability by fetal radiation exposure in rats

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The immature brain in the central nervous system is sensitive to ionizing radiation, and develops at adult stage, microcephaly disorders including mental retardation, attention deficit-hyperactivity disorder and cognitive dysfunction. We investigated the relationship between spatial cognitive impairment in the hippocampus and merge of ectopic neurons in adult rats that were prenatally exposed to X-ray irradiation. Adult rats receiving 1.5 Gy X-rays at embryonic day 15 showed significant learning disability in the water-maze task. According to the mean value of the swimming time, we categorized the irradiated adult rats into the following three groups: slightly damaged group, mildly damaged group and severely damaged group, but no significant difference in the brain weight was found between the three categorized groups. Ectopic neurons appearing at abnormal places were prominently observed in the hippocampus of the severely damaged group with a remarkable learning disturbance. Furthermore, we examined neural activity in hippocampal slices prepared from prenatal exposure to X-rays in rats. The spatial pattern of neural activity toward and through CA1 of the severely damaged group was similar that of the control rat, but the response was distinctly weaker, producing less voltage spread and amplitude. The number of acetylcholine receptors in rat hippocampus exposed to fetal stage was not changed in cerebral cortex, but significant decrease occurred in hippocampus. These finding suggest that the cognitive dysfunction induced by prenatal exposure to X-ray irradiation may be attributable to ectopic neurons of the hippocampus and the reduction of hippocampal neural activity.

Biology: Biological Differences between Carbon, Proton and Photons Poster Discussion Sessions

PTC58-0049

Cellular senescence induced by carbon ion radiation of hypo-fractionation

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Due to the unique physical and biological features, heavy ion therapy has been widely used in cancer treatment. It has been proved that hypo-fractionation technology is superior to the traditional radiation on curative effect for some solid tumors, such as liver and lung tumors. However, whether the hypo-fractionation of radiation increases the risk of heavy ion therapy needs to be further evaluated.

During the past four years of in vitro investigation, we found that a plenty of melanoma cells, breast cancer cells and normal fibroblasts went into tetraploid-senescence after carbon ion radiation when the single dose was higher than 5Gy. The results of senescence associated-β-galactosidase (SA-β-gal) positive cells showed that carbon ions were more efficient to induce senescence than X-rays under the same dose (5Gy), implying the high relative biological effectiveness of heavy ions. We revealed that the un-repairable DNA damage including double-strand-breaks, single-strand-breaks and base damage contributed to cellular senescence detecting by immunofluorescence hybrid technology. We also found that senescence was related to the long-term G2-arrest cells induced by exposure. Genes essential for G2-M transition such as Cyclin B1, Plk1 and Aurora were prematurely downregulated at both transcriptional and translational levels.

These findings will provide experimental and theoretical basis for the tumor treatment options from the radio-biological point of view. And the effects of secreted factors of senescent cells on the proliferation, genome stability and migration ability of non-radiated cells are being under investigation.

PTC58-0528

Study on the radiosensitivity of carbon ion(12C6+) beam to different lung adenocarcinoma cell lines

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Objective: To investigate the radiosensitivity differences of different doses of carbon ion radiation different types of lung adenocarcinoma cell lines.

Method: A549, H1299, H460, and H1975 cell lines were cultured in RPMI-1640 complete nutrient solution. Respectively using 0, 1, 2, and 4 Gy $^{12}C^{6+}$ heavy ion beam, delivered by Wuwei carbon ion therapy system, to irradiate 4 cell lines, which was Continue cultured to 24h and 48h, then to detect cell clone rate, cell inhibition rate, cell cycle, apoptosis respectively, and related molecules.

Results: The results of cloning formation test showed that with the increase of irradiation dose, the cell cloning formation rate was inhibited, and the inhibition effect was successively H1975, H460, A549, and H1299. The inhibition effect of 4Gy group was the most significant. The cell inhibition rate was successively H460, A549, H1299 and H1975, inhibition effect was significantly increased with the increase of irradiation dose ($p < 0.05$) at 24h, 48h and 72h. Flow cytometry analysis results showed that the cell cycle was significantly blocked in the G2/M phase after carbon ion beam irradiation, the blocking effect was successively H1975, H460, H1299,and A549. With the increase of radiation dose, apoptosis rate increased obviously. RT-PCR and immunofluorescence confocal assay showed that with the increase of irradiation dose, the expression levels of STAT3, e-cadherin, TGF-β1 and mmp-2 decreased accordingly.

Conclusion: Carbon ion beam can inhibit the proliferation of lung adenocarcinoma cells, and induce cells to G2/M phase arrest, so as to induce apoptosis and inhibit the proliferation and metastasis.

PTC58-0642

Gene expression of cancer cells in hypoxic and normoxic environment under irradiation

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Radiotherapy (RT) is one of the main approaches for cancer treatment used alone or in combination with chemotherapy where the main cellular target is nuclear DNA. We investigated how cancer cells (bladder, breast, brain, lung, prostate) react to radiation on a genetic level, where cells were treated with 6 Gy in normoxic and hypoxic conditions. The gene groups studied with qPCR included DNA repair, cell cycle, cancer stem cell markers, and metabolic genes.

In general, RT causes genomic damages, either directly by injuring the DNA, or indirectly, by ionizing water molecules, where radiation induces the formation of Reactive Oxygen Species (ROS). X-ray efficacy seems to be compromised by the presence of a Cancer Stem Cell (CSC) sub-population, which is radiation resistant. Moreover, there is mounting evidence that hypoxia changes cellular ROS levels and would protect DNA from oxidative damage and thus conferring radioresistance to CSCs.

Cells irradiated with X-rays in hypoxia show a decrease in the expression of the cancer stem cell marker genes accompanied with a downregulation of metabolic, DNA repair and cell cycle genes, while irradiation under the presence of oxygen causes upregulation of the previously mentioned gene groups. This leads to the conclusion that there is an underlying concept connecting the gene groups. Taking the concept of pathways to a more general approach, one can introduce an oxygen and no-oxygen depending pathway to describe the response of cancer generally to radiation. This work focuses on the effect of X-rays, which will set a baseline on the pathway-response in carbon-treatment.

PTC58-0069

Elucidating uncertainties in radiobiological parameters in proton beam irradiation by a global fit

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The relative biological effectiveness (RBE) is known to increase towards the end of the proton range as the linear energy transfer (LET) of the proton beam increases. A generic RBE factor of 1.1, as often applied to proton therapy treatment plans, may be inadequate in predicting the tumor response and the toxicity to the peripheral normal tissues. Better understanding of RBE as a function of LET is therefore crucial in ensuring the safety and efficacy of proton therapy treatments.

Recently, Abolfath et al. (Sci Rep 7: 8340, 2017) proposed a global fit to cellular survival curves across different LETs to reduce uncertainties in the fit and elucidate unphysical fluctuations of alpha/beta ratio in the function of LET. Our study used published datasets of V79 Chinese hamster lung fibroblasts and AG01522 normal human skin fibroblasts under proton beam irradiation and re-analyzed them with a single global fit across all LETs.

The R2 for V79 and AG01522 are 0.9760 and 0.9787, respectively. Figure 1 shows the data points and the fit for the two cell-lines studied. Figure 2 shows a plot of the RBE as a function of LET.

Our results showed that the global fit technique could be applied to other cell lines. Similar smooth transitions in RBE could be observed. Furthermore, the α/β ratio for V79 was calculated in the high LET region that was not established in the original work. This can lead to a better understanding of biological response of tissue towards the end of the proton range.

PTC58-0051

The radiosensitizing effect of Gadolinium oxide nanocrystals in NSCLC cells under X rays and carbon ions irradiation

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Gadolinium oxide nanocrystals (GONs) have been used as theranostic sensitizers in clinical radiotherapy study. In this study, GONs were employed to investigate their radiosensitizing effect in NSCLC cells. GONs caused hydroxyl radical production and oxidative stress in a dose- and concentration- dependent manner in NSCLC cells after X rays and carbon ions irradiation. The radiation enhancements of GONs reached 26.3% for the NSCLC cells under investigation at 10% survival level compared with irradiation alone (Figure 1). Further biomechanisms study demonstrated the presence of GONs enhanced the hydroxyl radical production, apoptosis incidence and autophagy incidence compared to irradiation alone. This study unravelled the radiosensitizing effect of GONs in NSCLC cells and presented the first evidence for GBNPs radiosensitization via activating the cytostatic autophagy pathway (Figure 2).

PTC58-0054

Dynamic recognition and repair of DNA complex damage

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Irradiation (IR) can be used to treat cancer by inducing complex and irreparable DNA damage in the cancer cells, which may lead to their apoptotic death. However, little is known about the molecular mechanism of this DNA damage. Here, the non-small cell lung cancer cell line A549 was treated with either X-ray or carbon ion combined with bleomycin (BLM). The cell survival rate, frequency of double-strand breaks, dynamic changes in γH2AX and p53 binding protein 1 (53BP1), and protein expression of Ku70, Rad51, and XRCC1 were determined by clone formation assay, agarose gel electrophoresis, immunofluorescence, and western blotting. The results showed that the most obvious complex double-strand breaks occurred in the carbon IR+ BLM group. The number of γH2AX and 53BP1 foci in the 0.5 h X-ray IR + BLM group was highest ($p<0.001$) among all the groups. γH2AX foci were detected in the nucleus at 0.5, 1, 2, and 4 h, but were distributed throughout the cell at 6 h after IR in the carbon ion IR + BLM group. The expression of Ku 70 increased and XRCC1 decreased at 2 and 6 h after IR. Our data indicate that a DNA damage frequency of 13.4/Mbp is caused by clustered DNA damage and further show a correlation between γH2AX, 53BP1, and XRCC1 levels and the extent of DNA damage. The results of this study provide insights into DNA damage recognition and a rationale for the clinical use of radiotherapy.

PTC58-0093

A single quality factor for all ion types? How relative biological effectiveness relates to various beam quality factors

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The relative biological effectiveness (RBE) is known to vary for different ion types and different beam qualities. A single beam quality factor (BQF) for all ion types will be valuable, as data from different heavy-ion radiobiological experiments can be aggregated for determination of radiobiological parameters while reducing the statistical uncertainties. Some proposed BQFs even provide a natural extrapolation of radiobiological parameters from photon experiments. Correlations between RBE and various BQFs are compared in our study to see which is the most suitable to quantify the beam in RBE experiments.

We investigated three BQFs: linear energy transfer (LET), Z^2/E and $(Z_{eff}/\beta)^2$, where the terms are defined in Table 1. The RBE with survival fraction of 0.1 as the endpoint was first calculated for four radiobiological experiments. A least-square linear fit was performed on the RBE versus BQF while restricting data with LET less than 100 keV/μm to avoid data-skewing due to the "overkill effect". The correlation is represented by the Pearson's correlation coefficient *r*. Table 1 presents *r* for the four cell lines studied. The fits are shown in Figure 1.

Our study shows that while Z^2/E may result in a bigger *r* for some cell lines (V79 and HSG, with a significant difference in only HSG), the advantage does not extend to all. $(Z_{eff}/\beta)^2$ exhibits a stronger correlation with RBE than Z^2/E for the T-1 cell line, but a weaker correlation than LET for all cell lines. LET remains the most natural choice as a BQF in heavy-ion RBE studies.

PTC58-0506

Repair of radiation induced damages of V79 cells after carbon ions exposure with different LET

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The high effectiveness of carbon ion radiotherapy has been clinically demonstrated. However, normal tissue responses to differing radiation spectra along a carbon ions Bragg curve, including its plateau, peak, post peak, are of great interest regarding both early and late possible effects. Repair of radiation-induced cell damages after carbon ions exposure is one of the most considerable radiobiological and clinical parameters. It depends on number of damages and LET of radiation and determines cell killing or cell surviving. Post-irradiation repair of damages induced by carbon ions (454 MeV/nucleon, U-70 accelerator, IHEP, Protvino) in Chinese hamster V79 cells was studied. Flasks with cells monolayer in the stationary growth phase were irradiated in a water phantom either in the plateau (LET ~10-12 keV/μm) or in the peak (LET ~180 keV/μm) of the pristine Bragg curve, thus simulating damaging normal tissues and tumor cells, respectively. The carbon doses were 6 Gy for the plateau and 1, 2, 3.5 Gy for the Bragg peak. During and after irradiation cells were in pure medium, after irradiation they were kept at 37°C for 0, 0.5, 1, 2, 4, 6, 8, 10, 12 h before reseeding in full medium, and incubated for 8-10 days for colony formation. No repair of damages induced by carbon ions in stationary V79 cells was observed during incubation times studied for each dose both at the plateau and the Bragg peak. The plateau data might be due to non-optimal conditions for post-irradiation repair and are of interest for future studies.

Oral Abstracts
Physics: Dose Calculation and Optimisation
PTC58-0131

New modalities for FRoG: Sandbox strategy applied to pelvic cancer patients treated with carbon ion therapy

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Purpose: To improve patient data analysis for carbon ion radiation therapy (CIRT) with an in-house built tool allowing for Fast dose Recalculation on GPU (FRoG). The relation between Relative Biological Effectiveness (RBE)-weighted dose (DRBE) and patient outcomes can be better understood if the impact of different RBE models (the Microdosimetric Kinetic Model (MKM), the Local Effect Models (LEM-I and -IV)) and the dose-averaged linear energy transfer (LETd) are made easily accessible. In this context, FRoG can serve as a sandbox environment for implementing advanced physical and biophysical models for CIRT.

Methods: Pelvic cancer patient plans, optimized with LEM-I, were recalculated with MKM and LEM-IV and LETd maps were obtained. The relation between different DRBE and LETd distributions and local control was investigated through target DVH comparison. MKM DRBE served for the evaluation of rectum Normal Tissue Complication Probability (NTCP) as described in Fukahori M et al.

Results: The average target median DRBE variation, with respect to LEM-I, was -15.23% for MKM prostate plans (16-fractions of 4.15 Gy(RBE) LEM-I). Average differences for sacral chordoma patients (16-fractions of 4.40 Gy(RBE) LEM-I) were -15.35% and -16.12% for LEM-IV and MKM. Highly inhomogeneous DRBE and LETd distributions were seen in the target. Rectum NTCP reflected the reported very low toxicity for the analyzed cases.

Conclusion: In this preliminary test, FRoG showed to be a powerful tool for CIRT patient data analysis, providing fast and integrated information still not available in the most of the commercial systems.

PTC58-0373

First report on validation of a Monte Carlo LET dose engine in a commercial treatment planning system

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Objective: To validate the first commercially available dose-weighted linear energy transfer (LET_D) dose engine for proton treatment planning.

Methods: Raystation (v5.99) was used to generate treatment plans in the CIRS-731 HN anthropomorphic phantom for three sites (brain, nasopharynx, neck) with a spherical target (Ø = 5 cm) with uniform target dose and calculated heterogeneous LET_D distribution, as expected.

In beam measurements were performed at our proton center (IBA) using a m^+-probe utilizing various silicon on insulator (SOI) microdosimeters capable of detecting lineal energies as low as 0.15 keV/um. Dose averaged mean lineal energy depth-profiles (γ_D) were measured for a 70 and 130 MeV spot in water and for the three treatment plans in the anthropomorphic phantom at various depths.

The measurements were compared to TPS LET_D calculations (1 mm voxels, Monte Carlo dose engine) in terms of a newly introduced gamma-index with 0.5 keV/um and 1 mm pass criteria for single spots and 1 keV/um and 2 mm for treatment plans.

Results: Measured γ_D and predicted LET_D were in good agreement for 70 and 130 MeV spots in water with a gamma pass-rates 85% and 87%, respectively (figure 1).

For the anthropomorphic phantom, gamma pass-rates varied for the brain (in target: 100%, distal edge: 37.5%), nasopharynx (target: 40%, distal edge: 100%) and neck (in target: 80%, distal edge: 40%) treatment plans (figure 2).

Conclusion: The accuracy of the TPS calculated LET_D distributions vary, however its clinical relevance remains to be further studied for site, voxel size and geometry specific conditions before clinical adoption.

PTC58-0207

RBE-weighted non-linear 4D-doses on CT-sequences depicting irregular motion

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Current 4D-treatment planning and simulations of scanned particle therapy are typically based on regular repetitions of the same 4DCT, failing to account for irregular breathing. We developed a method to compute non-linear RBE-weighted dose for sequential CT series.

LEM-based RBE calculation requires the complete particle spectrum for any given voxel with contributions from all motion phases. Dose warping as in linear dose calculation is therefore not possible. To enable an arbitrary number of motion phases, the dose calculation was modified to store RBE contributions into a CT-sized array. These arrays can then accumulate contributions from motion phases one after the other, followed by the non-linear dose calculation step when all motion phases are considered.

CT sequences of up to 500 CTs representing 4 min of irregular breathing were generated for human phantoms using the XCAT simulation software. Doses were calculated on the first repeated breathing period and compared to the new calculation on the entire irregular motion. Significant differences in the interplay patterns were observed, scaling with the simulated motion irregularity, as illustrated in the figure for a spherical lung tumor.

Breathing irregularity should therefore be considered when testing the robustness of 4D treatment plans or developing new mitigation strategies. The simulations are going to be confirmed experimentally. For patients, CT series can be generated from 4D-MRI, either offline or in the future also online in MR-accelerator combinations.

PTC58-0437

A hybrid dose approximation approach for robust optimization of Intensity Modulated Proton Therapy

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Purpose: To develop an approximation technique for computing the dose influence map during robust optimization for IMPT.

Methods: Our in-house robust optimizer for IMPT uses a fast GPU-based and Monte-Carlo-based dose engine. However, using the Monte-Carlo dose engine for all robust scenarios is time consuming and may not be necessary given the stochastic nature of range and setup uncertainties in IMPT. In this work, we propose a hybrid approach in which the dose influence map for the nominal scenario is computed using Monte-Carlo, while those for the robust scenarios are calculated through interpolation of the nominal dose. In order to take into account heterogeneity of the patient anatomy, interpolation is based on matching the water-equivalent path length along the beam direction. For fast implementation, all computations are done on GPUs.

Results: The method is tested on a small Ped-Orbit case with about 1000 spots and a large Head and Neck case with about 35000 spots. Range uncertainty of 3% as well as setup shifts by 3mm is considered. The DVH curves computed using the accurate Monte Carlo dose influence map for all scenarios are compared to those computed with the hybrid approach. Variations were found to be within 2-3%. In Figures 1 and 2, sample DVH comparison plots are shown.

Conclusions: A hybrid and fast approach for calculating the dose influence map for robust optimization of IMPT is provided. The given approach combines accuracy and speed. Differences at the level of 2-3% were observed when compared to the all-Monte-Carlo approach.

PTC58-0450

A FLUKA Monte Carlo code tool for RBE-modelling in proton therapy of hypoxic head and neck cancer

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Introduction: Hypoxic cancer cells are more radioresistant than well-oxygenated cells. This effect is quantified by the oxygen enhancement ratio (OER), which can potentially be included in calculations of the relative biological effectiveness (RBE) in clinical proton therapy. The aim of this project was therefore to create a FLUKA Monte Carlo code-tool which enables inclusion of OER-models in RBE calculations.

Materials and Methods: The Wenzl and Wilkens (2011) OER-model (WEN), with α- and β-values dependent on the linear energy transfer and oxygen partial pressure (pO_2), was adapted to an RBE-model using the linear-quadratic formalism. Positron emission tomography (PET) images, with [^{18}F]-EF5 as hypoxia tracer, of a patient with oropharyngeal cancer was used. pO_2-values were estimated voxel-by-voxel from the EF5-PET images, and a method for reading pO_2-values was implemented in FLUKA. Subsequently, a proton treatment plan optimized in Eclipse with prescribed doses 56/70 Gy(RBE) (PTV1/PTV3) was simulated in FLUKA applying the WEN model.

Results: Estimated pO_2-values from the PET-images showed varying oxygen levels in the PTVs (Figure 1). This was reflected in the RBE-weighted dose estimated applying WEN, which showed a hot spot in the high-risk area (PTV3) compared to dose calculations with RBE1.1 (Figure 2). The PTV1 median dose was 3% higher and the PTV3 maximum dose was 5% higher when applying WEN compared to RBE1.1.

Conclusion: An RBE-model including OER was implemented in FLUKA and presented RBE inhomogeneity in the target volume of a head and neck cancer patient. Such calculations may become useful in future clinical applications of hypoxia-guided particle therapy.

PTC58-0625

Evaluation of a calibration and correction algorithm for cone beam computed tomography image based proton dose calculation

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Purpose: Proton gantries with CBCT imaging systems are becoming more common. CBCT based dose calculation is challenging due to artifacts and lack of calibrated intensity values. One possible approach is deforming the planning CT (pCT) to the CBCT. However, deformation errors and unshared features, like air pockets, introduce range errors. This work evaluates a novel correction and conversion algorithm to enable accurate proton dose calculations on CBCT images.

Method: From a deformable registration an optimal CT to CBCT image value conversion table and a low frequency shading and artifact correction map are determined yielding a calibrated image (cCBCT). The algorithm was evaluated on prostate cases. The regions of interest (ROIs) where manually drawn on the pCT and the CBCT and ROI intensity statistics were used as one quality metric. The pCT was also deformed, both with (dCTcon) and without (dCT) these ROIs guiding the deformation. The CBCT ROIs were copied to dCTcon and dCT. Further, a range shift analysis was performed with the dCTcon dose as range reference.

Result: The pCT and dCTcon intensity statistics agree, justifying use of dCTcon as range reference. Both the dCT and cCBCT show small intensity and range differences, compared to pCT and dCTcon, respectively.

Conclusion: The results show that the proposed method performs equal to using a dCT. However, these cases contained no large unshared features nor anatomical changes, which would be detrimental for the dCT but pose no problem for the cCBCT. This indicates that the proposed algorithm presented here is preferred

PTC58-0653

Fast robust optimization using a patient-specific scenario selection methodology

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Purpose: Typical robust optimization strategies use pragmatic selection of treatment scenarios that limit considerably their ability to handle various types of errors in a statistically sound fashion. We propose a novel probabilistic scenario selection methodology that remedies these issues.

Material and Methods: Two successive steps are performed to pre-select the relevant optimization scenarios (later fed to a robust optimizer): First, 12 scenarios are chosen that cover 5 mm systematic setup errors (SE) and +/-2.5% proton range errors (PRE) (according to a 4D-isoprobability hypersurface defined by Gaussian distributions with sigma of 2mm and 1.6%, respectively). Second, 2 worst-case range error scenarios, estimated from maps of water-equivalent path lengths, are selected by sampling SE and PRE from the surface of the aforementioned 4D-hypersurface (Fig.1).

Treatment plans were calculated for a lung cancer patient using the open source robust optimizer MIROpt. The dose prescription was 60Gy. Conventional worst-case robust optimization with 5mm SE and +/-3% PRE was used as reference. Plan robustness was evaluated with the MCsquare dose engine by recalculating the dose distribution on a set of 100 randomly sampled error scenarios.

Results: The proposed method used only 14 optimization scenarios whilst achieving a similar plan in comparison with the conventional method (using 21 scenarios): average target coverage difference (D95) of approx 0.1Gy (Table1) and average lung V20 difference of approx. 0.3% (Table2) between both methods.

Conclusion: Using a statistically sound methodology, the scenario selection method reduces the number of scenarios, thereby accelerating the optimization process, and produces a robust treatment plan.

PTC58-0661

A WebGL based visual proton delivery simulator

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Introduction: Planning proton therapy is complicated because setup, organ motion, and range uncertainties affect dose delivery, dependent on beam directions and optimization. For robustness evaluation of plans, e.g. for training, a fast delivery simulator would be beneficial. For ease of use and access is should be web-based. The purpose of this project is to develop such a simulator.

Material and Methods: A full calculation is impractical, but using as core assumption that individual beams can move relative to each other, extremely rapid calculation of treatment scenarios is possible, that correctly render delivery variation at depth. We chose to implement the system on the GPU, using WebGL, where calculation is provided as C-like shader program, integrated in the web page code, that is evaluated massively parallel for every pixel on the screen. Input data (CT, contours and individual beam doses), are provided as a few large texture images (e.g. Fig. 1). Sliders allow setting the delivery and error parameters.

Results: The core of the shader program is only 50 lines. WebGL runs about 100 times faster than Javascript. Figure 2 shows a mock proton plan in the resulting web page; dose inhomogeneity due to range uncertainties per fraction is simulated. Calculation speed is high, even on a low end integrated graphic card, a 20-fraction treatment is simulated in 60 fps, allowing immediate feedback on a change of parameters.

Conclusions: Using WebGL it is possible to provide a realistic simulation of proton delivery. Evaluation of the simulation accuracy remains to be done.

PTC58-0531

Feasibility of predicting proton stopping power ratio using the MRI-measured material hydrogen density

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Purpose: Uncertainties associated with CT-derived proton stopping power ratios (SPR) are a limiting factor in exploiting the full benefits of proton therapy. We investigate the feasibility of a model that predicts SPR using MRI-measured material hydrogen densities.

Methods: A model (SPR-H) that related the medium's hydrogen density with its SPR was constructed by considering twenty-two materials taken from the National Institute of Standards and Technology (NIST) database. Subsequently, the model was used to predict the proton range and water equivalent thickness (WET) for nine tissue-surrogate materials of CIRS phantom, and the predicted values were compared with measurements using a multilayer ionization chamber (MLIC), as well as the treatment planning system (TPS) calculated WET. Additionally, a phantom setup was designed and irradiated and for each plug, ion-chamber measured dose was compared to the TPS dose calculations based on SPR-H model. For further validation, proton-density and T2-weighted MRI scans of twelve salt-water solutions with different salt concentrations (hydrogen densities) were used by the SPR-H model, and the model-predicted SPRs were compared with their corresponding MLIC measurements.

Results: MRI pixel values of both scans correlated well with the measured SPRs. For all salt-water solutions and tissues-surrogates (except lung), model predicted SPR and WET were within 3% and 2% of the measurements and TPS predicted values. Additionally, the SPR-H predicted and measured doses were within 1.5% agreement. Larger deviations of 9% for SPR, and 2.6% for dose were observed for lung-tissue.

Conclusion: SPR predicted by SPR-H model can facilitate dose calculation while reducing range uncertainty in proton therapy.

Physics: Absolute and Relative Dosimetry
PTC58-0034

Stopping-power ratios and beam quality factors for carbon ion beams: Impact of new ICRU90 key data

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Reference dosimetry for carbon ion beams relies on calibrated ionization chambers and dose-to-water-based protocols (IAEA, 2006). The recent update of dosimetric key data (ICRU, 2014) impacts the computation of beam quality correction factors, k_Q. We present a detailed assessment of the carbon stopping-power ratio water to air, $s_{w,air}$, for carbon beams in a wide range of reference conditions and updated k_Q factors.

Monte-Carlo radiation transport simulations using the Geant4 toolkit (Agostinelli *et al,* 2003) were used to compute $s_{w,air}$ fully implementing the new recommendations from the ICRU Report 90. Both monoenergetic carbon ion beams (3 to 30 cm range in water) and spread-out Bragg peaks (SOBP) of different widths and depths were considered.

The $s_{w,air}$ at the reference depth of 1 g cm^{-2} in water for the reference conditions of monoenergetic carbon ion beams fall into a (–0.07 %,+0.12 %) interval around $s_{w,air} = 1.1247$. As for the reference conditions of the center of physically optimized SOBPs, $s_{w,air}$ fall into a (–0.09 %,+0.18 %) interval around $s_{w,air} = 1.1274$. If a single constant $s_{w,air}$ is used as recommended in TRS398, an average between the values representative for pristine and physically optimized SOBP configurations should be used, which is 1.126. All values obtained in this study fall into a (–0.2 %,+0.3 %).

The updated beam quality factors agree very closely with experimental data for cylindrical chambers (Osinga-Blättermann and Krauss), especially where updated Co-60 perturbation factors were available. For plane-parallel chambers, however, discrepancies up to 2 % were found which require further investigation.

PTC58-0052

A real-time neutron fluence measurement system for boron neutron capture therapy (BNCT)

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Boron neutron capture therapy is a treatment modality that utilizes nuclear reactions between ^{10}B atoms and neutrons. The dose delivered to a patient is directly proportional to the number of nuclear reactions, which is a function of neutron fluence. Accordingly, accurate measurements of neutron fluence is a determining factor in the quality of the neutron beam. The current gold standard for fluence measurements in BNCT is the Au radio-activation method. This method, however, is an offline, time-consuming method. To advance BNCT, we are developing a real-time neutron fluence measurement system (NeuFluenT). The detector in this system consists of a smalll grain Eu-doped LiCaAlF6 scintillator, an optical quartz fiber, and a photo-multiplier tube. This detector is capable of discriminating neutrons from gamma rays without significantly perturbing the neutron field. In this study, we evaluated the dependence of the system response on the neutron flux to check whether this system can be applied to an in-phantom BNCT neutron field measurement, where the flux ranges from 10^8 to 10^9 n/cm^2/s.

Neutron fields were produced by the Neutron exposure Accelerator System for Biological Effect Experiments (NASBEE) at the National Institute of Radiological Sciences. The results indicate that the system response is stable over the range of flux observed in a water phantom exposed to a BNCT beam. We envision that our system will be utilized to check beam output constancy as well as in-phantom neutron distributions calculated by a treatment planning system.

PTC58-0232

Dosimetric evaluation of high throughput mouse proton irradiation for spinal cord toxicity

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Background: Recent clinical evidence of enhanced relative biological effectiveness (RBE) near the proton Bragg peak (BP) resulting in brainstem necrosis in pediatric patients indicates the need for continued investigation. A number of *in-vitro* studies have shown increased RBE at the end of proton range. However, *in-vivo* studies have been limited due to the complexity of accurate dosimetry and dose delivery. The purpose of this investigation was to create a precise method of treating the mouse spinal cord with various portions of the proton Bragg curve for quantification of proton RBE.

Methods: Mice were restrained in 3D printed acrylic boxes, shaped to their external contour, with a silicone insert extending down to mold around the mouse (Fig. 1A). Brass collimators (Fig. 1B) were designed for parallel opposed beams to treat the spinal cord while shielding the brain and upper extremities of the animal. Two plans were generated using either the entrance or the BP portion (Fig. 2A-C). Positional uncertainty was assessed by collecting a library of live mouse scans (n=2, 4 independent scans each) and comparing dose volume histogram statistics (D90 and V90). Dosimetric evaluation and LETd calculations were done using EBT3 radiochromic film (Fig. 1C,E,F) and our in-house GPU-based Monte Carlo, respectively.

Results: Preliminary results from the mouse library showed the average D90 and V90 to be 92.17% and 99.80%, respectively, suggesting a fairly robust setup. Film analysis showed the dosimetric uncertainty to be $+0.6\%$ and $+2.2\%$ for the entrance and BP plans, respectively.

PTC58-0282

Development of RALPH (proton RAnge Length PHantom) for proton range audit

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One of the largest sources of uncertainty and a major limitation in particle therapy is the treatment planning system (TPS) range prediction. This uncertainty is due to inherent computed tomographic (CT) uncertainties which affects the TPS. This work aims to quantify experimentally the range error with an in-house built geometric phantom including radiochromic films (EBT3). RALPH is made of solid water, which has previously been optimised to be water-equivalent for light-ion beams, as well as lung and bone substitutes. The phantom is made of 10 cm x 10 cm slabs with a length of 12.5 cm. RALPH allows the insertion of different configurations of materials (0.5 cm slabs of solid water, bone and lung) in front of the radiochromic film to measure the impact on the proton range. Experiments have been performed with a 115 MeV proton mono-energetic scanning beam to measure the range for seven different configurations of the phantom. Each different configuration was also scanned at the proton center to obtain a 120 kV CT image. Film results show a measured range shift of around 10 mm when comparing a solid water including 10 mm bone slab (range with bone configuration was 95.2 $\pm$ 0.2 mm) against a solid water with 5 mm lung slab (range with lung configuration was 105.5 $\pm$ 0.1 mm) configuration. Experiments will be compared with calculated ranges from the TPS via CT images. This work will inform the development of a full range uncertainty audit for proton beams.

PTC58-0310

Experimental evaluation of fluence correction factors for absolute dosimetry of high-energy-scanned proton beams

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The new IPEM Code of Practice being developed for dosimetry of proton beams will recommend that ionization chambers are calibrated directly in the user beam against the NPL portable primary-standard graphite calorimeter, where calibrations will be performed in composite (box) fields of homogenous dose. The quantity measured in graphite calorimetry is absorbed dose-to-graphite; thus, conversion factors need to be derived to determine absorbed dose-to-water. In this work, fluence conversion factors, *kfl*, between water and graphite were measured to convert from one quantity to the other. Experiments were performed at the 226MeV proton cyclotron at the Trento Proton Therapy Center, Italy. Fluence correction factors were measured by the ratio of ionization chamber readings in water and ionization chamber readings in water after passing through various thicknesses of graphite at water-equivalent depths, *zweq*. Two beam configurations were used: 10x10x10cm^3 volumes of homogenous dose centred at depths of 10cm and 25cm in water. The *kfl* increased with depth because the total nonelastic nuclear interaction cross section per atomic mass are larger for graphite than for water and it could be approximated by a linear fit in function of depth, $kfl \approx 0.0017 \cdot zweq + 1.0004$ and $kfl \approx 0.0021 \cdot zweq + 0.9971$, for the box fields centred at 10cm and 25cm, respectively. At the depths of interest, in the middle of the composite fields where calibrations will be performed, *kfl* are higher than 2.5% and thus need to be considered for reference dosimetry. This work will contribute to the implementation of a new Code of Practice for absolute dosimetry of high-energy-scanned proton beams.

PTC58-0353

Wide-range LET measurements of primary and secondary charged particles in ion radiotherapy with the Timepix-3-pixel detector

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The purpose of this work is to measure the linear energy transfer (LET) spectra of primary and secondary charged particles produced in particle radiotherapy environments using the Timepix-3 detector. The data are valuable for benchmarking of existing Monte Carlo (MC)-based treatment planning systems that calculate the LET distributions for biologically-weighted treatment plan optimisation. There is great interest in using LET distributions to identify regions of higher than average LET and concentrate them in the tumor while avoiding healthy tissue. Using a single compact Timepix-3 detector, we measure the composition, spatial and spectral characteristics of mixed radiation fields produced in water-equivalent phantoms of varying thicknesses at the HIT (Heidelberg) and HIMAC (Chiba) ion therapy facilities. The ASIC-based Timepix-3 detector (Fig. 1) provides quantum-imaging sensitivity and visualizes the track of each individual particle and its 3D direction, allowing LET determination for a wide range of heavy and light charged particles, including energetic and minimum ionizing particles in addition to low-energy, high-LET particles. Utilising integrated readout electronics (AdvaPix-TPX-3 camera) and the control/readout software Pixet, the LET distributions of particles will be registered over a wide LET range, Fig. 2, and for various beam depths.

PTC58-0448

Prompt gamma spectroscopy for the determination of density and elemental compositions of samples irradiated by ion-beams

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Particle therapy with protons and ions of Helium, Carbon and Oxygen, features the highest clinical potential in terms of efficacy and effectiveness. The prompt gamma (PG) radiation emitted during irradiation allows for a real-time range monitoring due to its nearly-instantaneous emission. Moreover, it has been demonstrated by Polf *et al.* that it is possible to determine the concentration of Oxygen within tissues irradiated with proton beams by measuring ^{16}O (6.13 MeV) PG emission. We aim at generalizing this technique to other beam species, such as the ones accelerated at the Heidelberg Ion-Beam Therapy Center (HIT). We irradiated five samples with different densities and Oxygen and Carbon concentrations in order to verify the correlation with the prompt gamma production from specific reaction channels. We confirmed the results obtained with proton beams and observed new features for the other beam species. There are significant differences in the cross-sections for the high-energy and low-energy prompt-gamma emissions. The lighter particle beams (Fig. 1) show a better correlation in the high-energy region (above 3 MeV) and the heavier particle beams (Fig. 2) in the low-energy region (below 3 MeV). Fig. 1 shows an enhanced intensity with an increasing Oxygen concentration of the PG emission from the interaction of the Helium beam with ^{16}O (5.2 and 6.13 MeV). Conversely, there is an intensity enhancement with an increasing Carbon concentration of the PG emission from the interaction of the Helium beam with ^{12}C (4.44 MeV) and from the interaction of the Oxygen beam within the low-energy region.

PTC58-0498

Compact low-voltage/power helium-free detectors for neutron dosimetry at hadron therapy facilities

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We have constructed watertight neutron probes, shown in Fig. 1, for measuring in-situ neutron fluence inside water and anthropomorphic phantoms used in proton therapy. Our probes are networked in arrays of compact, low power, low pressure basic cells with configurable attachments for determining neutron energy and momentum, with a voxel resolution of 5x5x10 mm^3. Within a basic cell, neutron absorption in a thin film of boron-10 produces energetic alpha and lithium-7 particles inducing scintillations in a noble gas. This scintillation is detected by a solid-state silicon photomultiplier (SiPM). A basic cell can be packaged in a volume of a few cubic centimeters, operated at atmospheric pressure, consuming $<$20 mW, and is powered/analyzed via a standard USB connection. We have compared our cells' performance with that of conventional helium-3 detectors; their performance is competitive with respect to both neutron detection efficiency and insensitivity to gamma radiation. The small footprint and low power of the basic cell makes feasible the design of neutron probes for dosimetry measurement of charged particle therapies. Figure 2 shows Geant4 simulations of the neutron and proton dose in a water phantom at the Maryland Proton Treatment Center (MPTC). Unlike the localized proton dose, the neutron dose is spatially diffuse, and is strongest near the point of entrance of the proton beam, where MeV neutrons have high relative biological effectiveness. We have performed neutron dosimetry using this design at MPTC and will present measurements at the conference.

PTC58-0657

Development of tools for the calculation of correction factors for a proton calorimeter

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The National Physical Laboratory (NPL) is currently commissioning a graphite calorimeter as a primary standard of absorbed dose to water for clinical proton beams that is robust and portable enough to be used in the end-user facility. The aim is to achieve an uncertainty on reference dosimetry of 2% (at 95% confidence level), based on a draft IPEM UK Code of Practice (CoP). It will utilise the NPL portable graphite calorimeter and enable the provision of direct absorbed dose to water calibrations in proton therapy centers, using clinical SOBPs. Different standard test volumes recommended in the CoP have to be simulated in order to calculate the non-graphite ($k_{non\text{-}g}$), gap (k_{gap}) and volume averaging (k_{vol}) correction factors for the proton calorimeter. The ‘‘primary’’ STV in scanned beams for reference dosimetry is a 10x10x10 cm3 dose volume centerd at 15 g cm-2 depth in water, with ‘‘secondary’’ STVs with the same volume defined to be centerd at 10 cm and 25 cm depth in water. To create these volumes, a tool has been developed using Matlab for the optimization of the weight of the individual beamlets (previously obtained with TOPAS Monte Carlo simulations) to achieve the required depth profile ($<$0.5% uniformity in the SOBP region). The tool has been further optimized to calculate the corrections including experimental fluctuations and trends, in order to retrieve all the uncertainties for the final uncertainty budget. This work will significantly contribute to the establishment of the NPL graphite calorimeter as a primary standard in proton therapy.

Physics: Image Guidance

PTC58-0525

Evaluation of the clinical benefits of MRI-integrated proton therapy

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Introduction: Accurate image-guidance plays a critical role in improving current proton therapy (PT) protocols. We aim to assess the clinical benefits of integrating MRI and PT and compare the toxicities with the alternative available image-guided methods for treatment of liver cancer.

Methods: Ten patients with liver tumors who underwent serial MRI scans were retrospectively selected. The reduction of PTV margins due to real-time (integrated) and offline MRI-guidance were qualified by examining the anatomy and setup accuracy using the MRI data, and quantifying other uncertainties, e.g. tumor delineation and motion. Proton treatment plans were created for: (1) conventional, (2) offline and (3) real-time MRI-guided (MRiPT) scenarios (figure-1). Normal tissue complication probability (NTCP) of uninvolved liver was compared for relevant endpoints to assess the clinical impact of margin reduction.

Results: Random setup/anatomy uncertainty was found to be 1.25mm. Assuming motion prediction, systematic lag-time between imaging and treatment was replaced by 1.5mm random motion modeling uncertainty. The resulting residual margin was 3mm isotropic on MRI-defined GTV. Liver NTCP was significantly decreased for Child-Pugh score changes (C-P)(up to 48%) and grade$>$3 liver enzymatic changes (LEnz)(up to 23%), for MRiPT compared to conventional (CBCT-guided) PT (figure-2). Differences between NTCP in scenarios 2 and 3 were up to 17.7% for C-P and 1.6% for LEnz. NTCP reduction between scenarios 1 and 3 was on average 5% larger for PT than VMAT.

Conclusion: Clinical benefits of MRiPT are potentially significant and exceed that of CBCT-guidance and offline MRI. Larger NTCP reduction is achieved by MRiPT than VMAT (MR-linac).

PTC58-0297

Quantification of inter-fraction setup uncertainties in image-guided particle therapy at Italian National Center for Oncological Hadrontherapy (CNAO)

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Purpose: Image-guided evaluation of setup uncertainties should be performed on institutional basis since commercial solutions or consensus guidelines are not yet consolidated in particle therapy.

Although partial communications on setup evaluation have already been presented, we comprehensively report positioning accuracy of 1392 patients (20505 fractions) treated between 2012-2018.

Materials and Methods: CNAO features different image-guidance systems: in two rooms a stereoscopic imaging system acquires two oblique projections at isocenter, whilst a third room is equipped with a customized robotic solution that offers out-of-isocenter orthogonal projections [1,2].

Patients are immobilized using multiple combination of devices. Kilo-voltage x-ray images are acquired and rigid 2D-3D image registration is performed. The resulting setup correction vector (CV) is applied to the robotic patient positioning system featuring 6 degrees-of-freedom motion capabilities with translational/rotational accuracy of 0.3mm/0.1°[1].

Such CVs were retrospectively collected and grouped by treated anatomical site according to the Union of Light Ion Therapy Centers in Europe recommendations [3].

Results: Table1 shows patient and treatment data. The range of the CVs is reported in Figure1. The median translations in right-left and superior-inferior direction were found to be lower than 1mm. An exception was observed in the superior-inferior direction in the lower abdominal group with 5.2mm median value. A trend toward posterior and anterior direction was observed in supine and prone treatments, respectively. The magnitude of this displacement is explained by differences between simulation and treatment couches.

Conclusion: This extensive analysis evaluates the adequacy of setup uncertainties quantification for plan robustness assessment or safety margins definition. [1]doi:10.7785/tcrt.2012.500386. [2]doi:10.1016/j.ejmp.2014.10.075. [3]doi:10.1016/j.radonc.2018.04.027.

PTC58-0624

Optimization and performance evaluation of a proton computed tomography system for small animal imaging

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Proton computed tomography (pCT) can potentially reduce range uncertainty in proton therapy inherent in the semi-empirical conversion of Hounsfield units into relative stopping power (RSP).

We report on the development of a pCT detector system for pre-clinical small animal imaging. It is based on low material-budget Micromegas tracking detectors and a time projection chamber with Micromegas readout structure containing Kapton absorbers functioning as range telescope. To safeguard ideal operation close to intrinsic performance limits, a geometrical optimization of the system components was conducted. Therefore, FLUKA Monte-Carlo (MC) simulations were performed for an accurate in-silico detector model using proton beams of clinical-like properties. In addition, the overall imaging capabilities in terms of spatial resolution and RSP accuracy were evaluated using dedicated phantoms.

Experiments with 22MeV protons from a tandem accelerator using a small-scale detector prototype (Figure 1) demonstrated the feasibility of the proposed system. MC simulations estimated a proton trajectory reconstruction accuracy of better than 0.4mm for a geometrically optimized tracker configuration, resulting in a spatial resolution of around 0.2mm. Usage of 500μm thick Kapton absorbers yielded a range accuracy close to the range straggling limit, corresponding to sub-1% RSP accuracy for most tissue-equivalent materials (Figure 2).

We have developed and optimized a cost-effective pCT system with accurate imaging performance for pre-clinical research. Future work aims at quantifying the dosimetric improvement related to pCT for small animal proton therapy treatment planning. This work has been financially supported by the ERC Consolidator Grant SIRMIO (ID:725539).

PTC58-0671

Reduction of range uncertainty in particle treatment planning enabled by patient-individual stopping-power prediction using dual-energy CT

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Purpose and Objective: Comprehensive assessment of range uncertainties in particle treatment planning for a dual-energy CT (DECT) based direct stopping-power prediction (DirectSPR) suitable for clinical implementation.

Material and Methods: The DirectSPR approach, thoroughly validated in prior work and jointly implemented with Siemens Healthineers in a prototype, is characterised by a patient-size dependent model calibration and patient-individual consideration of tissue variability. Uncertainties of this DECT-based approach were quantified regarding image acquisition, modelling and miscellaneous sources (Fig.1) and propagated to the overall range uncertainty via the GUM guideline (Guide to the expression of uncertainty in measurement). Model calibration and validation was based on a multitude of CT scans for phantoms with varying geometries. The resulting overall uncertainty was determined for different clinically relevant tumor entities, separated into an absolute term (for five treatment sites) and a term relative to the particle range (for head, lung and pelvic region).

Results: The relative range uncertainty was 1.7%, 2.0% and 2.0% for the head, lung and pelvic region, respectively. The absolute term was between 2.5mm (brain) and 3.5mm (head and neck, pancreas). In comparison to the safety margin currently applied in treatment planning based on single-energy CT (3.5%+2mm), the overall range accuracy is increased for beam paths with a water-equivalent thickness above 30mm (70mm) in the head (body) region (Fig.2).

Conclusion: The uncertainty in particle range calculation is reduced by patient-individual DECT-based stopping-power prediction. The obtained range uncertainties are directly applicable to the currently ongoing clinical implementation of DirectSPR for routine treatment planning at our institution and will result in a dose reduction in normal tissue.

PTC58-0573

Surface imaging for treatment geometry virtualisation and collision detection in proton therapy

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Image guided proton therapy is an automated treatment in which the patient position is set remotely using a robotic arm. Such an approach allows for high precision alignment but raises safety concerns due to possible patient collisions. As such, time-consuming treatment simulations without the patient often need to be performed. Alternatively, such simulations can be virtualized using equipment models and standard patient avatars (IDCAS, medPhoton). In this study, we investigate the use of hand-held surface scanners to morph a patient avatar to the real patient geometry for precise collision detection predictions.

For this, we have compared two systems, the Artec Eva and Microsoft Kinect V2, which use stereovision of structured light and time-of-flight technology respectively. The accuracy of the two systems has been tested in a therapy setting using an Alderson phantom, a vacuum pillow and a bite block. Surface scanning was performed free-hand while walking around the treatment couch, hence avoiding occlusions and shading issues. Multiple surface patches were combined using Artec studio, and then registered onto the reference body contours of the phantom, as extracted from CT data, using an iterative closest point algorithm. Median distances between surface imaging and CT after registration were 8.6mm (IQR: 11.7mm) and 5.5mm (IQR: 7.5mm) respectively for Eva and Kinect, with highest values at surface concavities.

Our results confirm the suitability of hand-held surface scanners to build a 3D model of the patient and immobilisation devices that is accurate enough for collision avoidance and evaluation of air gap to the nozzle.

PTC58-0670

Low-dose cone beam CT (CBCT) for paediatric image-guided proton therapy (IGPT)

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Introduction: Accurate set-up is essential to prevent geometric miss in proton therapy (PBT). Daily CBCT image-guidance is more reluctantly applied in paediatric patients due to concerns over imaging dose. Optimising low-dose CBCT imaging protocols for children would help alleviate imaging dose concerns and allow for accurate treatment delivery. This work aims to simulate low-dose CBCT for the Varian ProBeam CBCT system, allowing design of optimised imaging protocols without the need to acquire additional scans.

Method: An ATOM newborn phantom was scanned using low-dose CBCT exposures ranging 35-548mAs (0.035-0.548mGy). The signal-noise relationship was measured and used to add Gaussian noise to the 548mAs projection images prior to reconstruction, simulating low-dose scans. Simulation accuracy was assessed by comparison of SNR in the simulated and acquired projection images. Accuracy of patient set-up using low-dose scans was assessed by comparing bony anatomy registration, using the 548mAs registration as the gold standard.

Results: Fig. 1 compares the SNR of the simulated and acquired low-dose scans, showing a strong agreement and maximum discrepancy of 0.44%. Fig. 2 compares the 548mAs scan to the simulated and acquired 35mAs scans. Although noisier than the high-dose scan, low-dose scans showed clear bone/soft tissue boundaries, with a maximum registration discrepancy of 1.02mm.

Conclusion: Low-dose CBCT scans for PBT image-guidance was effectively simulated by addition of noise to projection images prior to reconstruction. This allows for assessment of low-dose imaging exposures with no additional dose burden. Preliminary results show that image registration remained accurate even at the lowest available dose and opens up further investigation using patient data.

Physics: Beam Delivery and Nozzle Design

PTC58-0173

Novel toroidal configuration for hadron therapy gantry

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GaToroid is a novel fixed toroidal gantry, based on superconducting magnets, able to deliver the dose at discrete number of angles with neither rotation of the magnets nor the patient. The basic principle is to use the axial-symmetric magnetic field between each pair of coils constituting the torus to bend and focus accelerated particles down to the isocenter. A *vector magnet*, an upstream bending magnet, rotating or combined vertical/horizontal, is used to steer the particles into the gantry with a proper angle, depending on the beam rigidity and the required angle of treatment.

2D particle tracking has been integrated in the magnet design to optimize the coil geometry and field profile, aiming to precise beam focusing at isocenter in the whole range of treatment energies with steady-state toroidal field. Furthermore, 3D particle tracking in vacuum has been developed to simulate the beam and reconstruct the transfer matrix of this unique shaped Gantry. Angle deviations can be properly applied by the vector magnet to perform beam scanning around the isocenter, without the need of classical downstream scanning systems.

Large acceptance, steady-state configuration and superconducting magnets offer interesting reduction of size, weight and cost of gantries and related infrastructures, creating an attractive alternative to the state-of-the-art.

PTC58-0090

Innovative silicon detectors for measuring the energy of clinical proton beams: Preliminary results

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The MoVeIT project of the INFN is investigating the use of innovative silicon detectors optimized for time resolution (Ultra Fast Silicon Detectors - UFSDs) to assess the beam energy of clinical proton beams. The capability to detect single protons and the outstanding time resolution provided by UFSD technology (tenths of ps for 50 micrometers thick sensors) are exploited to measure protons' time-of-flight (TOF). The latter is calculated as the difference of protons' time-of-arrival in two UFSDs in a telescope configuration, using the constant fraction algorithm. From measured TOF values, the corresponding beam energies are obtained through an analytical approximation validated with Geant4 simulations, taking into account the energy lost in the air between sensors. The preliminary results, obtained with two UFSDs (80 micrometers active- and 150 micrometers total-thickness; 3x3 mm^2 area, each) at relative distances ranging between 4 and 97 cm on a clinical proton beam with energies between 62 and 228 MeV, showed an error smaller than 1 MeV (at 228 MeV, 97 cm) in the energy estimation. Following these encouraging results, dedicated strip sensors were designed, produced and thinned to a total thickness of 100 micrometers, in order to cover an area of 4x4 mm^2. Computational simulations are ongoing to study the best combinatorial methods to identify coincidences among strips, and new beam tests have been planned. The proposed device could monitor the beam energy online, and also estimate the accelerator precision in changing energy, which is essential to investigate future developments towards tumor tracking strategies.

PTC58-0230

The TOPAS tool for particle simulation: Facilitating studies of creative ideas for Monte Carlo based research

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TOPAS wraps and extends the Geant4 Simulation Toolkit to make advanced Monte Carlo (MC) particle transport simulation easier to use for medical physicists and radiation biologists. It has recently become part of the US NCI's initiative "Institute for Technology in Cancer Research (ITCR)". TOPAS is free and well supported for all non-profit users in medical physics and radiation biology worldwide. TOPAS currently has 579 licensed users at 236 institutions in 36 countries.

Unlike any other MC simulation tool, TOPAS lets users create entirely novel setups from adjusting minor details to modeling whole new therapy and imaging machines with no need to learn any programming language. All aspects of simulation are controlled from a unique system of control files, the TOPAS Parameter Control System. An optional GUI makes setup even easier.

In this presentation we will show how, ten years into the TOPAS project, we have achieved our goal to provide a tool that can be of tremendous help for clinical as well as research physicists. Further, we will demonstrate how TOPAS is being used:

- for modeling treatment delivery systems
- for calculating dose in patients
- for quality assurance in a clinical environment
- for four-dimensional beam scanning applications
- for detector design studies
- for microdosimetry applications

PTC58-0022

Monte Carlo simulations and dose measurements of a patient-specific 3D range-modulator for proton therapy

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Purpose: To develop and validate a novel 3D range-modulator for very fast treatment of moving targets. In contrast to pencil-beam scanning, where the multiple iso-energy layers are associated with relatively long irradiation times, the 3D modulator uses only one single energy to create a homogeneous and highly conformal 3D dose distribution, decreasing extremely the treatment time.

Methods: Extending previous extensive research, a 3D modulator was now developed from a real CT patient data. A lung tumor with a complex 3D contour and irregular distal/proximal edges was chosen to simulate a worst-case-scenario.

The 3D modulator consists of many fine pyramid-shaped structures (pins) with 4 mm^2 base area and different heights (Fig.1). The modulator was optimised for 151.77 MeV ^1H and manufactured on a high-quality 3D-printer. The FLUKA Monte-Carlo package was used to calculate the resulting dose distribution. Additional high-resolution 3D dose measurements were conducted at the Marburg Ion-Beam Therapy Center.

Results: There is very good agreement between the measured and simulated dose. Fig 2. shows a homogeneous dose distribution conformed not only to the distal, but also to the proximal edge of the target.

Conclusion: Utilizing state-of-the-art 3D-printing technique to manufacture complex modulators is possible. Combining the advantages of very short treatment time, the 3D range-modulator could be an alternative to treat lung tumors with the same conformity as full raster-scanning treatment.

PTC58-0620

Development of high dose rate rapid scanning system for breath-hold treatment for proton therapy

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Purpose: SHI has developed a high-speed scanning treatment system which enables us to irradiate the treatment volume within one breath-hold time, less than 15-20 seconds. This system contributes to expand the scope of irradiation for moving target in case of the treatment of breath-hold. The purpose of this article is to summarize the design and evaluations of the high-speed scanning treatment system for proton therapy.

Methods: SHI has introduced the method of continuous line scanning to achieve higher dose rate and shorter delivery time. Furthermore, SHI has improved the response time of energy selection time by updating the energy degrader in the beam transport line, the control system and power supply system. These techniques can enable to minimize the energy selection time during the irradiation for proton therapy

Results: The performance test of the new system, called the fast layer switching system, has been conducted on site. And we have confirmed that all the requirements items are satisfied within the specification without any errors. The time of layer switching time can be less than 300ms by each layer and it can make it possible to complete the scanning irradiation, for example 1litter volume with 20 layers, within the 15.6 seconds.

Conclusions: SHI has developed short time proton therapy system with the fast layer switching for moving target treatment. And this system provided treatment as of November of 2018; SHI is also preparing to start for moving target by the treatment in one breath-hold.

PTC58-0652

Energy-dependent apertures for improved conformality in collimated pencil beam scanning treatments

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The use of apertures has become increasingly common in the delivery of pencil beam scanned (PBS) treatments where sharp edge gradients are desired to protect sensitive organs at risk. However, when using a machined, patient-specific aperture for this purpose, the treatment plan is limited to specifying a single aperture curve for each field. This aperture is drawn to be conformal to the maximal cross section of the tumor volume over all of the energy layers in the field. This does little to make the field conformal at depths where the tumor volume boundary may lie well within the aperture curve.

With the recent introduction of commercially available multileaf collimators (MLCs) designed specifically for PBS, treatments can now be planned with a different aperture curve for each energy layer. This results in improved conformality and sharp lateral penumbras over the entire tumor volume. However, new capabilities of the treatment planning system (TPS) are required.

The RayStation 8 TPS includes an algorithm that automatically generates aperture curves conformal to projections of a target onto surfaces of constant radiological depth. We will present calculated doses for both simple geometric and clinical treatment plans using this feature. We will also present measured results of such treatment plans delivered on a Mevion HYPERSCAN system that uses its Adaptive Aperture proton MLC to perform energy layer specific [SR1] collimation.

The results demonstrate some surprising physics consequences of using energy-dependent apertures, for example demonstrating interesting ways in which lateral collimation can improve distal conformality.

Physics: 4D Treatment and Delivery
PTC58-0147

Quantitative analysis of treatment process flow using real-time-image gated-spot-scanning proton-beam delivery log system

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Purpose: Motion management is important in spot-scanning proton-beam therapy. By using a real-time-image gated-spot-scanning proton-beam therapy (RGPT) system, we can irradiate with high accuracy a moving tumor such as Lung, Liver, Pancreas, and Prostate. However, it would be predicted longer treatment time in RGPT system compared to the traditional case without using gating function that scheduled 30-min per session. The aim of this study is to assess the patient throughput and gating efficiency for RGPT system.

Materials and methods: Data from 190 patients, corresponding to 261 treatment plans and 4659 sessions performed from October 2016 to November 2018, are included in this study. We quantitatively analyzed the treatment process flow, the difference between the ideal beam delivery time which simulated from synchrotron accelerator operation pattern and the actual treatment beam delivery time, and the gating efficiency in RGPT patient from machine log system.

Results: Among all treatment plans, 112 cases (42.9%) used the gating function. The mean and standard deviations of treatment process flow of RGPT system were 30.0 +/- 7.4 min per session which include the beam delivery time 7.3 +/- 4.7 min. The difference of the beam delivery time per field were 1.2 +/- 1.9 min with gating function and 0.4 +/- 0.3 min without gating function, respectively. The results of the gating efficiency were 42.5% (Lung), 38.2% (Liver), 30.1% (Pancreas), and 81.9% (Prostate), respectively.

Conclusion: Even with a gating function, our results demonstrate that the treatment schedule for one session can be 30-min slot per session.

PTC58-0534

Breath-hold plan reproducibility in intensity modulated proton therapy treatment

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Purpose: The breath-hold technique minimizes target margins and improves normal-tissue sparing in proton radiotherapy. We investigated the reproducibility of breath-hold plans in intensity modulated proton radiotherapy (IMPT) using frequent quality assurance CT scans (QACTs).

Methods: Eighteen consecutive patients with thoracic or upper gastrointestinal malignancies treated with the voluntarily breath-hold spirometry system (SDX, Dyn'R, France) were analyzed. Reproducibility of the breath-hold plans were assessed using 1-3 QACTs per patient by re-calculating the initial treatment plan on each QACTs. To evaluate the reproducibility of each patient plan, variations in dose-volume histograms (DVH) for target and OAR volumes were examined on QACT plans relative to initial CT plan. To show the degree of spread in QACT parameters relative to the initial plan, the error window (EW) required to cover the 95th percentile variations for each structure was reported.

Results: 4% and 7% EWs were observed with respect to CTV1 (initial, 18 patients) and CTV2 (conedown, 7 patients) volumes. EWs for D95%, maximum, and mean dose of CTV1 were 1.4%, 6.6%, and 1.5%, respectively. For maximum OAR doses, the required EWs were: small bowel (1.2Gy), large bowel (1.5Gy), heart (7.6Gy), and spinal cord (5.5Gy), whereas a 4.4% EW was observed for lung V20. Similarly, EW for OAR specific mean doses were: liver (1.2Gy), stomach (0.7Gy), kidney (0.1Gy), heart (1.5Gy) and esophagus (3Gy).

Conclusion: Mean target volume and OAR doses for patients planned using breath-hold scans are reproducible to within 5% of the prescribed dose. Clinical implications of these findings should be examined prospectively.

PTC58-0614

Assessment of two techniques for respiratory motion-suppression in lung cancer treatment with proton therapy using MRI: A clinical study

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Introduction: With the aim of minimizing motion during treatment of thoracic tumors, two potential motion-suppression strategies are being investigated in healthy subjects as part of an on-going clinical trial: Short-term apnoea with extended deep inspiration breath-hold (eDIBH) vs high frequency percussive ventilation (HFPV) for apnoea-like suppression of respiratory motion. The effectiveness and reproducibility of both techniques is being compared using MRI imaging.

Materials and Methods: eDIBH is based on pre-DIBH hyperventilation with 100% oxygen while HPFV uses high-frequency, percussive pressure pulses to assure gas exchange without active breathing. For each volunteer 4 $\times$ 2 1.5T MRI imaging sessions are being performed at weekly intervals using both eDIBH and HFPV, accompanied by daily breath-hold training over a 3 weeks' period. To quantify inter-fractional changes, lung-distance-metrics were defined, consisting of one reference point (spinal cord, Ref_SC) and four lung structure points (apex, carina, vessel, diaphragm) [Figure1]. The study aims to investigate 20 healthy volunteers.

Results: Results of the first 4 subjects show a positional reproducibility of 0.8-3.9mm for eDIBH and 0.8-10.1mm for HFPV. The corresponding relative positional errors (StdDev/Mean) for all lung structure points range between 0.3-3.5% for eDIBH and 0.4-14.4% for HFPV [Figure2]. Maximum eDIBH durations range between 217 and 423sec.

Conclusions: Both techniques for suppression of respiratory motion are practicable. Preliminary results however indicate a better reproducibility concerning the consistency of internal lung-metrics for eDIBH than HFPV. In addition, since eDIBH duration can be extended to 3 minutes or more, it could be feasible to completely deliver individual treatment fields within a single eDIBH.

PTC58-0130

A model for RBE-weighted dose estimation in irregularly moving targets

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Purpose: We propose and test a model for dose estimation in irregularly moving targets treated with scanned carbon-ion beams.

Methods: The model requires 3D-CT information and consists of four steps: (i) scanned delivery during free breathing is simulated, (ii) the reference CT is transformed in a water-equivalent depth (WED) space, where maps of physical dose and radiosensitivity parameters (α, β) are translated according to tumor motion, (iii) transformation back into CT coordinates generates perturbed maps, (iv) RBE and RBE-weighted dose distributions are estimated. The plan was optimized on the reference CT, then the estimated 4D dose (Estim) was compared to the ground truth 4D dose (GT) obtained using the 4DCT and deformable image registration. Six breathing curves were simulated for each plan. The validation was performed in a digital phantom and a pancreas patient (Figure.1A). For the latter, the model was tested on: the clinical 4DCT (regular), a synthetic 4DCT with doubled motion amplitude (x2), and a set of synthetic 4DCTs representing tumor baseline shifts (bls).

Results: Maximum tumor motion and gamma pass rates are reported in Table.1. In the phantom study, the tumor D95% was 4.2Gy(RBE), 0.9Gy(RBE), 0.6Gy(RBE) in the plan, GT, Estim, respectively. Figure.1B-D display DVH metrics differences for the patient case.

Conclusion: Results show that motion effect is appreciable, and the WED-space model gives consistent estimations of dose alterations even though anatomical deformations are not explicitly modeled. The model is suitable for testing plan robustness to respiratory motion different from that depicted in the 4DCT and arbitrary irregular motion.

PTC58-0377

Mechanically-assisted and non-invasive ventilation can improve the motion management strategies while treating thoracic or upper abdominal tumors with proton therapy

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Background and Objectives: Proton therapy of mobile tumors faces many uncertainties given their breathing-related motion, but also the proton range variations within the crossed tissues and the interplay effect that can unpredictively distort the dose distribution. Mechanically-assisted non-invasive ventilation (MANIV) could stabilize breathing with the volume-controlled (VC) mode, reduce amplitude with the shallow-controlled mode (SH) or mimic prolonged breath-hold with the slow-controlled mode (SL). Patient's tolerance and tumor motion reproducibility were evaluated in this trial.

Material and methods: In lung, liver and breast cancer patients, the tumor motion was assessed with MANIV and compared to spontaneous breathing (SP)(Figure1). All the patients underwent 2 dynamic MRI sessions with each breathing mode (Figure1). Tolerance was assessed through oxymetric analyses and questionnaires. The tumor/nipple motion was tracked and analysed within each MRI and between MRI (intra- and inter-session reproducibility).

Results*:* Twenty patients (49-83 years old) were included (Table 1). They all tolerated MANIV very well. The breath rate (BR) was always more stable in VC/SH than in SP. With SH, the motion amplitude was reduced of 0.6mm to 9mm proportionally to the BR increase (1.5 to 3.4-fold increase). With SL, the breath-holds were as stable as in SP in terms of range within a same plateau (0.9mm) or position between plateaus (0.2mm). Breath-holds in SL lasted on average 16,7sec.

Conclusion: MANIV and its different ventilation modes offers exciting perspectives for motion management in proton therapy. MANIV may thus be proposed in clinical practice for different dedicated applications (reduced margins with SH, breath-hold with SL, gating with VC or SL).

PTC58-0692

Using a mixed helium/carbon treatment beam for monitoring intrafractional motion

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Adding a percentage of helium ions to a carbon ion therapy beam has recently been proposed for online range monitoring: at the same velocity, the two ions have approximately the same magnetic rigidity which enables their simultaneous acceleration, but helium has approximately 3 times the range of carbon ions. In this work, we investigate this modality for monitoring organ motion with a novel range detector in experiments at the Heidelberg Ion-Beam Therapy Center (HIT).

As first step, the feasibility of the method was investigated with simple phantom geometries. Unfortunately, a mixed beam cannot be generated with the current HIT setup. Hence, the beam was mixed artificially by irradiating a carbon SOBP plan twice - using helium as beam particle in the second run and mixing the runs in data processing. The beam was monitored with a novel range telescope consisting of a stack of thin (2-3mm) scintillator sheets read out by a flat panel CMOS sensor developed at University College London.

Preliminary results indicate that the system can monitor the helium range despite the contamination by carbon fragments when using a factor 10 less helium primaries compared to carbon. In case of air gaps in the treated volume, the system's fast data acquisition enabled online observation of changes in the helium range. The technique is expected to be most useful for treatment monitoring in cases subject to random motion, as e.g. bowel gas movements. Further work will focus on the verification of the technique for complex anthropomorphic geometries.

Physics: Commissioning New Facilities

PTC58-0213

A retrospective comparison of effect of reductions in energy switching times on center capacity

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Introduction: To quantify how a software upgrade (R7 to R8) changed beam delivery times and impacted efficiency and capacity.

Methods: A 4-room center treating ~90 patients/day, treating for ~7 years with optimized operations, underwent a software upgrade which reduced energy and room switching times from ~30 and ~4 seconds to ~20 and ~0.5 seconds respectively. The center uses RFID data to track patient treatments and has software which links this to beam delivery data extracted from the treatment log server. Two 4-month periods, July-Nov in 2017 and 2018, with comparable patient volume, representing periods before and after the software change, were retrospectively analyzed.

Results: A total of 16168 and 17102 fields were analyzed 2017 and 2018. For bilateral head and neck and prostate patients, the beam waiting time was reduced by nearly a factor of 3 and the beam delivery times were reduced by nearly a factor of 2.5 (Fig. 1). Room switching times were reduced more modestly from 0.51±0.49 to 0.32±-0.37 minutes (Fig. 2). Capacity in our gantry has increased from approximately 30-35 patients to 40-45 patients in a 16-hour daily operation. For nearly constant patient volume, the center has been able to close an inclined beam line which has reduced beam competition.

Conclusions: Many proton centers are striving for increased efficiencies in operations by reduction of QA time, treating daily alternating fields, and simplifying IGRT processes. We demonstrated that reductions in energy and room switching time can significantly increase center capacity. Further reductions are possible and encouraged.

PTC58-0363

Is single-energy CT still an up-to-date standard imaging modality in proton therapy?

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In proton beam therapy, a single energy CT (SECT) is still the standard for treatment planning. Dual energy CT (DECT) and in-room cone beam CT (CBCT) are used in few centers. In our facility, proton patients are scanned with a Siemens Drive and a medPhoton Imaging-Ring is available for in-room daily CBCT.

We commissioned our CT scan for SECT and DECT using tissue-equivalent inserts with varied scan parameters to quantify the potential variations in Hounsfield Units. The relative stopping power (RSP) of each insert was also measured at our Mevion S250i proton unit. We investigated whether a sufficiently accurate RSP map can be obtained from SECT and DECT images in our proton treatment planning system.

A variation in the RSP prediction of 1% was determined for the bone inserts. In the soft tissues, RSP variations up to 2% were observed. Comparable results were obtained for the lung tissue surrogates. Our results also show that the CT calibration curve resulting from the stoichiometric method and the one obtained by simple interpolation of the experimental data differ by only a few percent. We further evaluate the deviations of the RSP values investigating the influence of scanning parameters (e.g., beam hardening correction) and algorithms, to quantify if the resulting range shifts are of clinical relevance. We will finally report on our work regarding the introduction of pseudo mono-energetic CT, DECT, and CBCT in the proton treatment workflow quantifying the clinical gain reachable through these imaging modalities.

PTC58-0416

Neutron dosimetry, radioprotection and shielding verification in commissioning of compact proton therapy centers (CPTC) using MCNP6 code and experimental measurements

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Introduction: Compact Proton Therapy Centers (CPTC) is referred to facilities with a single treatment room. The goal of this work is to carry out neutron dosimetry and shielding studies by estimating ambient dose equivalent H*(10) around CPTC facilities, aiming to protect the radiation workers and the public. Experimental measurements will be compared with values obtained with Monte Carlo calculations in order to develop the commissioning of the facility.

Methods: H*(10) due to stray neutrons in CPTC was calculated using Monte Carlo methods through MCNP6 code and CAD designs and models. The facility modeled is made up of a superconducting proton accelerator room and a treatment room with a rotating gantry. Several models of the radiation sources and the facility were simulated, starting from the manufacturer's model, with conservative assumptions, followed by models recently published with more realistic assumptions, and finally by models with more efficient shielding materials against neutron radiation. Experimental measurements will be carried out with extended range rem meters, WENDI-II and LUPIN-II types and conventional detectors.

Results: Using the more conservative assumptions a maximum H*(10) value obtained was 0.4 mSv/year around the accelerator room. In models based on more realistic and accurate assumptions, the results are even lower. Absolute responses of extended range REM meters used in the experimental measurements have been previously characterized.

Conclusions: The shielding effectiveness against diffuse neutron radiation in CPTC facilities has been verified with MCNP6, using different models, materials and assumptions of radiation source. In any case, results achieved are below internationally accepted dose limits.

PTC58-0472

Commissioning of the ProNova gantry and fixed beam rooms for first patient treatments at the Provision CARES Proton Therapy Center

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The ProNova SC360 is a multi-room proton therapy system utilizing permanent and superconducting magnets to reduce cost and size. Patient treatments using the SC360 Fixed Beam Treatment Room at the Nashville PCPTN have been underway since October 2018 and ProNova's proprietary superconducting gantry is in operation. The SC360 pencil beam scanning system was first used for patient treatments in February 2018 at the Knoxville Provision CARES Proton Therapy Center (PCPTK). At the Nashville (PCPTN) site (Figure 1) 5 patients were treated on the first day of operation ramping to 10 and then 15 patients in three weeks, the fastest proton therapy startup of any system to date. In parallel with clinical operation of more than 20 patients per day, the second treatment room in Nashville is being commissioned and is scheduled to be treating patients clinically on the superconducting gantry in early 2019. All rooms use a 6 degree of freedom robot combined with an integral couch based CBCT for patient imaging and positioning. Bringing the first superconducting proton gantry treatment room into clinical readiness will be the focus of this paper.

PTC58-0634

Will your facility shielding be adequate for new treatment techniques?

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Shielding for neutron production from passive scattered proton systems has been extensively investigated, and more recently updated for PBS. The introduction of FLASH irradiation and proton arc treatments requires reconsideration of traditional proton shielding methodologies. Facilities designed to accommodate traditional proton beams may satisfy long-term personnel exposure limits, but the brief instantaneous radiation fields produced by these technologies may pose radiation risks that have not been well characterized or considered in the course of regulatory development. Regulations and recommendations for defining instantaneous dose rate are highly variable worldwide and internationally accepted benchmarks applicable to these technologies have yet to be accepted within the community. We perform a review of applicable regulations and shielding methodologies used in the proton community to better define their applicability to new technologies. Techniques that integrate modern quantitative solutions with facility design and clinical workflow are illustrated as a step towards standardizing expectations of both designers and regulatory agencies. These methods provide a framework allowing the end-user to better understand the unique radiation fields associated with these technologies and the requirements to integrate them with existing, or newly designed, facilities.

PTC58-0713

Beam model matching of the low-dose PBS spot halo with and without a range-shifter at a multi-room facility

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Purpose: Nowadays, vendors at multi-room PBS facilities are capable of delivering ‘‘matched’’ rooms, offering clinics the prospect of scheduling patients flexibly because, in principle, the same beam model may be utilized for all. However, while matching is typically done at the primary spot sigma level, the residual unmatched low-dose spot ‘‘halo’’ can limit the successfulness of this endeavor. Here, we demonstrate a method to best handle the halo when deriving a beam model unified across multiple rooms.

Method: The variation in output with field size at the center of uniformly-irradiated energy layers is sensitive to the underlying spot shapes (Figure 1). Measurements of this variation are presented for spots in air in three different PBS rooms at our facility. The measurements span field-sizes of 40–250 mm, energies of 100–225 MeV, and were repeated with and without a 75 mm thick range-shifter (Figure 2). From these, the best unified, inter-room model of the low dose halo was derived.

Results: For beams without the range-shifter, careful modelling of the spot halo enables output in air to be predicted to within ~2% for all field sizes and all rooms; this improves the higher the energy. Agreement to with ~1% can be achieved, even in the worst case, when the range-shifter is included.

Conclusion: Measurements of output variation with field size, coupled with judicious determination of parameters characterizing the halo, can be used to maximize the accuracy of a unified, inter-room beam model. Interactions in the range shifter dilute inherent differences between the rooms.

Physics: Adaptive Therapy
PTC58-0366

An automated replanning strategy for near real-time adaptive proton therapy

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Purpose: To develop a method to automatically adapt treatment plans in near real-time to the anatomy-of-the-day for prostate and cervical cancer.

Material/Methods: Starting point is a prior plan optimized on the planning CT. First, spot positions (Bragg peaks) from the prior plan are restored by adjusting the energy of each pencil-beam to the water-equivalent path length in the daily CT. Subsequently, to compensate for deformations of target and OARs, pencil-beams are added followed by a pencil-beam weight optimization using the Reference-Point-Method. This method generates a Pareto optimal plan for the anatomy-of-the-day, with similar trade-offs to those in the prior plan. The method was evaluated using 8-10 daily CTs of 11 prostate cancer patients (88 CTs) and 3-4 daily CTs of 5 cervical cancer patients (19 CTs). Evaluation was done by comparing for each CT a full multi-criteria optimization without time constraints (benchmark) to the proposed method and to a forward dose calculation of the prior plan on each CT (no replanning).

Results: The figures show large dosimetric differences between no replanning and benchmark, while the differences between the proposed method and benchmark are substantially smaller. The use of replanning improved target coverage to clinically acceptable levels in 85/88 CTs and 19/19 CTs for prostate and cervix, respectively. All plans showed reduced OAR doses. Replanning took on average 2.9 and 3.6 minutes for prostate and cervix, respectively, using ~50% for dose computation.

Conclusions: The automation and realized replanning times make the proposed method an important step towards real-time adaptive proton therapy.

PTC58-0403

Deep-learning-based relative stopping power mapping estimation for CBCT-guided adaptive proton radiotherapy

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Purpose: Compared to helical CTs, cone beam CTs (CBCT) have less accurate Hounsfield Units and degrade image quality, limiting their potential use for proton dose calculation. In this study, we developed a learning-based approach to accurately estimate relative stopping power (RSP) from to daily CBCTs, to enable future CBCT-guided online proton dose evaluation and adaptive proton planning.

Methods: We first built a set of multiple paired training images including dual-energy CT (DECT) acquired for treatment planning and CBCT captured during the first treatment fraction. Then a deformable CBCT-DECT registration was performed to reduce anatomical differences between the images. The RSP mapping was generated using physics-based dual-energy approach to serve as training targets (ground truth). We used a cycle-consistent generative adversarial network framework with integrated residual block minimization to learn the nonlinear mapping between CBCT and DECT-based RSP map. This CBCT-based RSP generation algorithm was tested with 22 head-and-neck cancer patients with a leave-one-out cross-validation method. Mean absolute error (MAE), mean error (ME) and normalized cross-correlation (NCC) were used to quantify the differences between DECT-based and estimated RSP maps.

Results: The average MAE and ME were 0.056 ± 0.012 and -0.005 ± 0.031 between DECT-based and CBCT-based RSP maps, and the mean NCC was 0.965 ± 0.009 for all patients.

Conclusion: We have developed a novel learning-based method to generate accurate RSP mapping from daily CBCT imaging and demonstrated its reliability. The absolute value agreement and image similarity between DECT-based and CBCT-based RSP maps warrant further study and development of a CBCT-guided adaptive workflow for proton radiotherapy.

PTC58-0550

Towards the clinical implementation of Daily Adaptive Proton Therapy (DAPT): Implemented key-steps to reach the goal

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To fully exploit proton therapy in the presence of anatomical changes, it is advantageous to adapt the treatment based on daily 3D-imaging, acquired just before the start of the therapy. For this, an ultra-fast workflow is required such that adaption can be performed and validated in a few minutes. This is the aim of the DAPT project at PSI.

To minimize re-planning time, optimization based on an analytical dose calculation (ADC) has been implemented on a GPU such that full re-planning and re-optimization can be achieved in $<$ 10s for typical cases. Excellent agreement between this ADC and Monte Carlo (MC) calculations have been found ($>$93% of voxels agree within $\pm$5%). Consequently, as dose differences due to anatomical changes are much larger than those between ADC and MC calculations (Figure 1), GPU implemented ADC's are computationally efficient and effective for ultra-fast adaption. Secondly, patient specific QA will be replaced by fast dose reconstruction based on machine control files, which we have shown to be much more sensitive to potential parameter transformation errors than measurement-based verifications (Figure 2). Finally, *off-line* dose accumulation will be performed using log-file driven MC dose re-calculation based on the daily patient image. This step guarantees, over a slower time-frame (i.e. between fractions), dose accumulation based on the most accurate dose calculation engine and most recent patient anatomy.

In conclusion, many procedures for ultra-fast, effective and accurate plan adaption have been developed and implemented at our institute, and first proof-of-principle experiments are planned later this year.

PTC58-0005

Compartmental analysis of washout effect in rabbit brain: In-beam PET measurement using 11C and 15O beams

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Positron emission tomography (PET) is a practical tool for real-time verification of hadron therapy. In-beam PET imaging can be used to track the evolution of irradiated particles in living tissue. The biological-washout of the positron emitters, which is considered as a prohibiting factor of dosimetry, has a potential usefulness as a diagnostic index that provides a unique opportunity to probe the status of tumor viability, but the modeling for this has not been established. In this study, we measured washout-rates of rabbit brain and performed kinetic analysis on dynamic PET data to explore the biological-washout mechanism.

Six rabbit brains were irradiated by ^{11}C and ^{15}O ion beams, and time activity curves on the whole brains were obtained with our original in-beam-PET-prototype (Fig.1). The washout rate was obtained based on the two-compartment model, where efflux from tissue to blood (k_2), influx (k_3) and efflux (k_4) from the first to second compartments in tissue were evaluated (Fig.2).

The observed k_2, k_3 and k_4 of ^{11}C were 0.086, 0.137 and 0.007 min^{-1}, and those of ^{15}O were 0.502, 0.360 and 0.007 min^{-1}, respectively. This analysis suggested permeability of a molecule containing ^{11}C atoms might be regulated by a transporter because the k_2 was relatively low compared with a simple diffusion tracer. The k_2 of ^{15}O was comparable with ^{15}O-water. The k_3 of ^{11}C and ^{15}O were much higher than k_4 values, thus part of ^{11}C and ^{15}O ions were fixed in the tissue. This study provided useful data for modelling the biological-washout effect.

PTC58-0104

To replan or not to replan? That is the question: How frequently is adaptive replanning needed for PBS proton therapy?

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Background: Pencil Beam Scanning (PBS) proton therapy (PT) delivery allows for more conformal and homogeneous dose distributions than traditional Uniform Scanning (US) or Passive Scattering (PS) proton therapy. However, because of this additional precision, these dose distributions are less forgiving to changes during a course of treatment. The purpose of this study was to see how frequently PBS plans needed to be adapted over a specific time period, and which treatment sites required the most adaptation.

Methods: 1020 patients were treated with PBS PT at the NM Chicago Proton center from January 2016 to June 2018. Of these patients, 71 or 7% required one or more adaptive replans during their treatment course. Full information was available for review on 53 patients that are on PCG-REG001-09.

Results: See attached chart for specific treatment sites evaluated and percentages of adaptation per site. Rescan evaluation frequency per site for our facility will be discussed. The number of total rescans ranged from 1-6 and number of adaptive plans per patient ranged from 1-4. The most prevalent treatment site requiring an adaptive replan was head and neck with 21 out of 53 patients.

Conclusion: PBS proton therapy plans require frequent evaluation to ensure that the original plan robustness is maintained throughout the course. Head and neck, prostate, and brain were the top 3 sites requiring adaptation in this cohort. Despite the use of robust optimization, these PBS plans still required adaptation, with significant changes in patient anatomy being the primary reason for the adaptation.

PTC58-0396

NTCP robustness evaluation in head and neck proton therapy: From treatment plan to delivery

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Purpose: To determine the variation in normal tissue complication probability (NTCP) throughout the treatment course due to patient set-up and anatomical changes.

Materials and Methods: 22 clinical head and neck patients received 70 Gy(RBE) in 35 fractions of robustly-optimised IMPT treatment with weekly repeat CTs (min. 6). Each repeat CT was rigidly registered to the planning CT and a dose re-calculation performed. Using deformable image registration, this dose was then warped onto the planning CT. The weekly CT dose distributions were then accumulated into a total treatment course dose. The NTCP for grade $\geq$ II dysphagia, grade $\geq$ II xerostomia and grade $\geq$ III tube feeding dependence were then calculated and compared to the planned NTCP. Plans with increased NTCP $>$ 2.0% were retrospectively adapted mid-treatment and compared to the actual delivered course. All registrations and dose calculations were performed within RayStation v6.1 (RaySearch, Sweden).

Results: Differences in delivered vs planned NTCP (see fig. 1) ranged from +9.7% to -2.4%. 4 patients had an NTCP increase $>$ 2.0% due to weight loss and/or tumor shrinkage. In each case, a mid-treatment plan adaptation was shown to reduce the difference significantly. In general, the organs most affected were those distal to the targets.

Conclusion: The estimated, delivered NTCPs are comparable to the calculated, planned NTCPs in the majority of head and neck patients treated with proton therapy. Patients with large anatomical changes during treatment would benefit from biologically driven adaptive re-planning to preserve predicted outcomes.

Physics: Treatment Planning
PTC58-0622

Introducing a 'Dirty Dose'-based optimization objective function to control linear energy transfer in targets and critical structures

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Purpose: To control linear energy transfer (LET) distribution for intensity modulated proton plans by an objective function based on the novel concept of "Dirty dose" as metric of high LET energy depositions to be avoided.

Methods: When it is known a priori that certain routes to energy deposition are undesirable, denoting the corresponding dose as "Dirty dose", we hypothesize that such knowledge could be utilized in plan optimization. In this work, we treated energy depositions at LET $>$ 3 keV/um in organs at risk (OAR) as undesirable. The "Dirty dose" and total dose were determined at the initial spot dose calculation prior to optimization. Both doses were used with standard dose objective functions in the Monte Carlo based optimization algorithm of the RayStation 6R research version. Plans were generated for phantoms and an intracranial patient case with brain steam and chiasm as OARs. For comparison, we optimized by penalizing dose averaged LET $>$ 3 keV/um in OARs and optimized by penalizing track-ends falling in OARs (see Traneus and Ödén, *IJROBP* **103**:755-765 (2019)).

Results: All three methods achieved similar reductions of LET in the OARs and virtually identical physical dose distributions.

Conclusions: The "Dirty dose" concept can be used to achieve LET reduction in OARs. The straightforward application with standard dose objective functions like max DVH etc. makes it technically attractable. Further, there is no need to, in case of LET objectives, consider a low dose weighting, or, in case of the track-end function to guess an achievable track-end fraction.

PTC58-0593

Proton computed tomography and proton radiography with a fast monolithic proton imaging system

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Purpose: A clinical proton imaging system should be simple, lightweight, easily scaled to large field sizes, operate at high speed to maximize patient throughput, and expose the patient to the minimum possible radiation dose for a given resolution. We have developed a system to produce images of proton stopping power by tracking individual protons before and after the patient and measuring the proton residual range after the patient.

Methodology: We have constructed a fully functional prototype of a proton radiography system fully exploiting proton path information and optimized for pencil beam scanning systems. An iterative algorithm produces images with spatial resolution given by the tracking accuracy.

Results: Our system setup and a resulting radiography imaging are shown in Fig. 1. A first test of our system for tomography using a continuously rotating platform and repeating scanning pencil beam pattern is shown in Fig. 2.

Conclusions: Our clinically realistic prototype is now producing accurate, spatially sharp proton radiography and proton computed tomography images.

PTC58-0018

Robust beam orientation optimization for intensity-modulated proton therapy

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We propose a novel framework for IMPT integrating robust beam orientation optimization (BOO) and robust fluence map optimization (FMO). The objective function consists of a dose fidelity term, a heterogeneity-weighted group-sparsity and a sensitivity regularization. The L2,1/2-norm group-sparsity reduces the number of active beams from the initial 1162 non-coplanar candidate beams, to between 2 and 4. The group sparsity is weighted by tissue lateral heterogeneity, preferring beams more resilient to setup uncertainties. The sensitivity regularization term improves beam robustness against range uncertainties as well as generating robust scanning spot map. This group-sparsity based integrated BOO and FMO framework with sensitivity regularization and heterogeneity weighting (SHBOO-FMO) was tested on two skull-base-tumor (SBT) patients and two head-and-neck (H&N) patients. Conventional CTV-based plans (Conv) with SHBOO beams or manual beams were compared for beam robustness. The dosimetry and robustness of SHBOO-FMO plan was compared against manual beam plan with CTV-based voxel-wise worst-case scenario approach (MAN-WC). With SHBOO method, the beams with superior range robustness over manual beams were selected while the setup robustness was maintained or improved (first two columns in Figure 1). The SHBOO-FMO plans achieved comparable robustness with the MAN-WC method (last two columns in Figure 1). Moreover, SHBOO-FMO better spared OAR compared with MAN-WC under nominal situation, reducing [Dmean, Dmax] by [4.10, 5.82] GyRBE on average (Figure 2). In conclusion, we developed a novel IMPT robust optimization method, which efficiently solved robust BOO and FMO in a unified framework, generating plans with good robustness and superior dosimetry.

PTC58-0029

MultiRBE: treatment planning for protons with selective radiobiological effectiveness

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Clinical protocols for proton treatment planning recommend a uniform value for radiobiological effectiveness (RBE) of protons of 1.1, despite ample evidence from in-vitro and animal studies that proton RBE increases with LET, causing tissues distal to the target to receive an enhanced biological dose. While several voices in the medical physics community advocate for variable RBE-based optimization, uncertainties in RBE models have prevented its implementation in clinical practice, since an overestimation of RBE could cause significant target underdosage.

We propose a mixed RBE model (MultiRBE), where a uniform RBE is used in the target contours to ensure an adequate tumor coverage with physical dose, but a variable RBE is used elsewhere. It was implemented in the treatment planning system matRad and three example cases were planned: a homogeneous phantom and prostate and a head-and-neck cases. The plans were evaluated in terms of physical dose coverage ($V_{95\%}$), RBE-weighted-dose in organs at risk and normal tissue complication probabilities, where prediction models are available.

The planning algorithm showed potential for reducing the biological dose in organs surrounding the planning target (37% reduction in RBE-weighted-dose in the phantom) and thus decreasing the probability for complications in normal tissue (by up to 62% in the prostate case and 37% in the head-and-neck patient). This was achieved without compromising the target coverage or homogeneity in terms of physical dose, as a result of a smarter redistribution of dose among the surrounding tissues with regard to the optimization constraints, independent of the validity of the RBE models.

PTC58-0185

A Flexible Treatment Planning Platform: Modular treatment planning to help ideas become reality

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Treatment planning systems are essential software components in the preparation of radiotherapy treatments. While experience with proton therapy grows worldwide so too does the availability of standardised software, however the desire to explore research ideas is ever-present and there is a necessity for research systems to remain a step ahead of readily available products.

At the Paul Scherrer Institute (PSI), we have been developing a modular, flexible research platform to support and nurture the variety of clinical and technical research endeavours we wish to pursue.

The Flexible Treatment Planning Platform (FTPP) is a treatment planning application largely programmed in Java and has a three-tier architecture. It can perform GPU-based fast optimisations and dose calculations in seconds and employs a number of open-source libraries for handling challenges such as DICOM or graphical rendering. FTPP employs modular design aspects to allow functionality to be easily expanded or exchanged for different research purposes and at different technical levels.

FTPP supports a full planning workflow with patient specific QA in PSI's Gantry2. The focus now turns to more innovative horizons, some yet unrealised clinically, such as 4D treatments, automated daily treatment adaptation, spot reduction, automatic treatment planning, machine learning, and line scanning.

The goal of this presentation is to introduce the vision and capabilities of this research platform to the wider proton therapy community. We wish to invite discussion on strengths and weaknesses and fuse potential collaborations.

PTC58-0110

MRI-only treatment planning approach for clipless ocular proton therapy

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Purpose/Objective: The aim is to develop an MRI-based treatment planning approach with dose-based gaze-angle optimization as part of a multicenter effort to develop an MRI-only workflow for Ocular Proton Therapy (OPT).

Material and Methods: High-resolution ocular images were acquired on a 7T Philips MRI using dedicated eye coil and protocols. Tumor and Organs-at-risk (OARs) were automatically segmented to generate a realistic 3D reconstruction of the patient's eye. A Treatment Planning System (TPS) was developed in-house using a semi-analytical broad beam algorithm for passive scattering integrating the 3D MR-based eye reconstruction (Figure 1). To optimize doses to OARs, a weighted-sum objective function was computed for each gazing angle, which also included an objective to penalize extreme gazing angles. Extreme gazing angles at the periphery of the field of view received the highest penalties. Weights could be adjusted to prioritize sparing of specific OARs.

Results: The new treatment planning approach has been tested on 12 patients. Tumor coverage was reached for all cases ($D_{95\%} > 95\%$). Figure 2 shows an example of the weighted-sum objective function for one patient in the range of clinically feasible gazing angles. In this example, weights equally penalized four parameters: mean dose to the lens, maximum dose to the optic nerve, mean dose to the vitreous body and the gazing angle.

Conclusion: An MRI-based TPS for OPT was developed with a tool to aid decision-making for OAR sparing. The TPS was successfully tested on 12 patients.

PTC58-0265

NTCP reduction via a novel split field IMPT treatment planning technique in head and neck cancer

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Purpose: To investigate the normal tissue complication probability (NTCP) reduction for IMPT head and neck (HN) proton plans with a novel split field (with and without range shifter [RS]) technique.

Materials and Methods: The minimum range at our Proton Therapy (PT) center is 4 cm WET. Our HN treatment planning class solution employs two posterior oblique (160°,200°) and two anterior oblique (40°,320°) fields with RS. We identified 11 class solution planned patients who did not qualify for PT based on the model-based patient selection approach. Treatment fields were split into two components: with RS for target depth <4 cm and without the RS for target depth >4 cm in order to sharpen the lateral penumbra. Patients were robustly re-planned (3% range and 5 mm shifts) for two scenarios: all beams and only posterior beams split. Plan robustness was evaluated using a Voxelwise MinMax approach, NTCP was used as a composite measure of the difference in plan quality between the class solution and proposed beam splitting technique.

Results: Seven and 8 out of 11 plans qualified for PT with the posterior-beams-split (Figure 1) and all-beams-split techniques, respectively. All plans maintained target coverage robustness while resulting in statistically significant lower NTCP values relative to conventional plans (Table 1).

Conclusion: The split fields technique sharpens the lateral penumbra and reduces NTCPs, with the most NTCP reduction already achieved by splitting only posterior beams. As a result, an increase number of patients would benefit from proton therapy based on the model-based selection.

PTC58-0510

A new treatment planning concept accounting for in-vivo range verification in proton therapy

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Introduction: Prompt gamma (PG) monitoring is widely investigated to reduce range uncertainties in proton therapy. The precision of the PG signal as surrogate of dose is however affected by tissue heterogeneities and counting statistics. Hence, a new treatment planning (TP) approach is proposed to account for this.

Materials and Methods: A research computational platform, combining Monte Carlo (MC, Geant4) pre-calculated pencil beams with the TPS engine CERR (A computational Environment for Radiotherapy Research), was employed. A TP is created using an extension of CERR (initial TP) and the spot-by-spot PG emission and dose distribution are obtained using MC. The proton range is then compared to the PG fall-off for each spot to identify spots with reliable PG-dose correlation. A new TP (re-optimized TP) is created and some "good-correlation" spots are boosted (i.e., increased in weight) to enable better PG detectability on those spots. Both TPs are then MC-recalculated and compared. The method is tested on 4 head&neck and 1 prostate tumor patients.

Results: Re-optimized and initial TPs are comparable in terms of dose distribution (D95 of tumor DVH agrees within 98%), dose averaged linear energy transfer distribution (maximum difference less than 1%), and found similarly robust to interfractional changes, while the re-optimized TP fulfills the set statistical conditions for reliable PG monitoring of the boosted spots. Advantages over other proposed methods such as spot aggregation will be discussed.

Conclusion: We have developed a new approach explicitly accounting for PG monitoring in the TP process.

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PTC58-0521

Monte Carlo evaluation of analytical dose calculation algorithms for clinical plans treated with pencil beam scanning proton therapy

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Analytical dose calculation (ADC) algorithms are still widely used for treatment planning in PBS proton therapy. However, with fast Monte Carlo (MC) algorithms becoming clinically available, the suitability of ADC for proton therapy has recently been questioned.

In this study, we recalculate a comprehensive set of clinical cases, all originally planned using our clinically used ray-casting (RC) ADC, using both MC (Geant4 using TOPAS) and a more conventional pencil beam (PB) ADC approach.

17 patients treated at PSI with tumors in different anatomical sites have been selected for recalculation due to their wide variability of tumor position and volume. Nominal (RC), MC and PB dose distributions have been compared based on $D_{95\%}$, $D_{2\%}$, $D_{50\%}$ and $V_{90\%}$ for target coverage, and using either $D_{2\%}$, D_{mean} or V_{xxGy} as comparators of OAR doses, depending on the OAR constraints defined as clinically relevant in the original plan.

Target indices between dose calculations, and over all cases, to within +/-2%, except for two cases in the thorax where maximum differences were -3.3%. For the OARs, all metrics agreed between -2.2% and 3.1%, except for a small structure where the $D_{2\%}$ was 4.5% higher when calculated with MC.

In the context of other uncertainties in proton and general radiation therapy, these results indicate that using ADC for clinical dose calculations may still be clinically appropriate, particularly for plan optimization where the high calculational efficiency of ADC can best be exploited. The final dose calculation can then be performed by MC if deemed necessary.

Physics: Quality Assurance and Verification

PTC58-0121

Independent dosimetry audit based on end-to-end testing in proton beam therapy

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A novel methodology for dosimetric E2E testing based on customized anthropomorphic phantoms holding different detectors was established at the ion beam therapy facility MedAustron (Austria) in collaboration with NPL (UK). Based on this methodology an independent dosimetry audit was applied to HollandPTC (The Netherlands) equipped with a Varian ProBeamv3.5 machine.

A homogeneous phantom and two anthropomorphic phantoms (pelvis and head phantom) were customized to allocate different detectors: radiochromic films, Farmer chamber and alanine pellets. During dosimetry audit, the phantoms were moving through the workflow as real patients to simulate the entire clinical procedure. All treatment planning steps were performed with RayStation v6.1 and v7.0 TPS available respectively at MedAustron and at HollandPTC. The alanine pellets and their read-out were provided by NPL. Corrections for the alanine "quenching" were derived by a Monte Carlo calculation implemented in a non-clinical version of RayStation TPS.

The dose to water determined with the ionization chamber in all delivered plans was within 2% of the calculated dose. Doses determined with the alanine pellets after correction for the quenching effect showed a mean deviation within 2% and a maximum deviation below 5% in the homogeneous (fig 1) and anthropomorphic phantoms (fig 2). Several audits at other facilities are planned in the near future and more results may be available at the time of the presentation.

Our experience shows that the developed procedures can be used to support implementation of upcoming new proton therapy facilities and may also serve as dosimetric credentialing for clinical trials in the future.

PTC58-0149

Are patient-specific QA measurements required?

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Purpose: Standard of practice suggests that all energy and fluence modulated patient portals be verified with a measurement. The benefit of traditional methods of QA for ensuring accurate treatments is, however, often questioned.

Methods: The requirements for accurately delivering portals were reviewed and compared with traditional methods of QA measurement. Modern beamline monitoring methods and calculational techniques (i.e. Monte Carlo) were also reviewed. In addition, comparisons between Monte Carlo calculations and measurements with a 2D detector array in a homogeneous phantom were performed for a variety of patient portals.

Results: Traditional methods of QA in homogeneous phantoms do not, by themselves, guarantee accurate delivery nor do they test the quality of the plan. Beam delivery has been shown to seldom be a reason for inaccuracy with redundantly-instrumented beamlines having feedback and a sufficient routine QA program. Gamma analysis of Monte Carlo calculations compared with detector array measurements showed an average point pass rate of 95% using a 2 mm / 2% criteria.

Conclusions: For modern delivery and calculational systems, after an initial surveillance period with a new beamline and treatment planning system, portal-specific measurements are only required for new treatment techniques and classes of portals that have shown inconsistent results.

PTC58-0219

Consensus statement on patient specific quality assurance from the 2018 PTCOG treatment efficiency workshop

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In December 2018, the Treatment Efficiency Subcommittee of PTCOG held a 2.5-day workshop to discuss the viability, benefits and possible shortcomings of using treatment logs for patient specific quality assurance (PSQA). The workshop was held in Knoxville, TN USA with participants from several different countries utilizing equipment from various vendors. A writing group was formed to collect, summarize, and write a report that represents the consensus of the participants. A risk analysis was performed along with detail look at the role of the radiation oncology information system, treatment planning system, delivery system, and the communication between those systems. In brief, the findings were as follows:

1. Log Based PSQA is the preferred method for routine PSQA. It requires less equipment and the mock up treatment can be tested in the exact same conditions of the patient treatment. Using bulky detector equipment in water tank often prevents delivering the mock up treatment at the nominal gantry angles for the fields. Furthermore, using log files can lead to adaptive proton therapy treatment where the treatment quality is assessed right after the delivery.
2. A fully independent secondary dose calculation is required and it is strongly encouraged that either the primary or secondary calculation is an accurate Monte Carlo dose calculation.
3. Quality assurance of the log data and all data transfer is required.
4. As part of good practice, if a new technique is introduced to the clinic, proper commissioning including phantom based measurements are required.

PTC58-0228

The expansion of proton clinical trial QA for NCI-funded trials

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The US has a thorough site qualification and credentialing program developed by the Imaging and Radiation Oncology Core (IROC) for NCI-sponsored clinical trials. This program has been specialized for proton therapy over the past 10 years into a robust assessment of proton centers' ability to deliver consistent and comparable dose in a multi-institutional clinical trial setting.

Some of the services offered by IROC are very standard, such as beam output audits, but other services are unique to the IROC program, such as anthropomorphic phantoms that move with a respiratory phase pattern, or the comprehensive on-site audit which provides a thorough review of the proton therapy clinical program and recommendations for practice improvements. Despite this being a US-run program, many proton centers around the world have sought out IROC's proton audit services. Services such as proton beam output checks, anthropomorphic phantoms, and on-site audits have been requested by international proton centers in eleven countries on three different continents. With the global expansion of our proton audit program, IROC is in a unique position to compare proton therapy treatment practices across many different clinical settings. So far, the results have shown good consistency. The average beam output check for international centers is 1.01 (σ 0.02, n=61), compared to 1.00 (σ 0.02, n=669) overall. The average phantom pass rate for international centers is 70% (n=10), compared to 73% overall (n=246). Through these audits, IROC is building confidence in global proton collaborations for clinical trial research.

PTC58-0278

A feasibility study of using digital tomosynthesis for stopping power estimation with scanning proton beam

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The CT to stopping power calibration remains one of the greatest uncertainties in proton therapy. Although recent introduction of DECT is capable of reducing the *relative stopping power* (RSP) uncertainty from 3.5% to 1.5%, it will be challenging to push below this limit due to the inherent difference in interaction between photon and proton. To overcome this, proton-based imaging modality was introduced. In this work, we will examine the feasibility of proton Digital Tomosynthesis (pDT) in determining RSP *of proton*. Unlike proton Computed Tomography (pCT) which requires dedicated hardware distinct from the current proton therapy system, pDT can be implemented in current therapy system for small target such as the head region. We have previously modeled our Proton Scanning Beam nozzle with GEANT4 Monte Carlo software and in this preliminary work, we will use this software to generate proton *radiograph* data at different projection angles of a phantom (with known density and composition) assuming ideal detector's response. Then, tomographic reconstruction was performed using algorithms in *TomoPy* (includes back projection and iterative methods) and the RSP is extracted. This simulation and reconstruction framework determine the theoretical upper bound of the image quality of pDT and the accuracy of RSP determination from pDT. Preliminary result of this work shows that 3D reconstructions of the phantom with limited projections (around 40) is possible but accurate determination of RSP needs to be optimized with respect to types of algorithms and the modulated proton depth-dose profile to limit the effect of range mixing and shifting.

PTC58-0332

Preliminary quality assurance results of the spot-scanning arc therapy delivery

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Purpose: Recently, a new module was developed on a clinical proton system to allow simultaneously delivering spot-scanning proton beam treatments while rotating the gantry. This study designed and implemented the first quality assurance (QA) procedure to evaluate the performance of this new spot-scanning proton arc (SPArc) treatment delivery.

Methods and Materials: A series of experiments was first performed to measure the basic beam characteristics under the arc delivery, including isocentricity, spot profiles, beam flatness and symmetry, and beam output. Subsequently, patient specific QA of a brain SPArc plan was performed to compare the measured and calculated dose distributions. Finally, the log file of the SPArc plan was analyzed and processed to reconstruct the actual delivered dose.

Results: All the basic beam characteristics, spot position accuracy within 1mm, spot size within +/-2%, beam flatness and symmetry within +/-3%, and output within 2% of the selected energies were confirmed within the clinical requirements in the arc delivery, similar to the results of the fixed gantry delivery in clinical settings. The patient specific QA results showed a good agreement between the measured and calculated dose distributions for the brain SPArc plan with the gamma index of 98.6% (3%, 3mm). The analysis of the log file confirmed the accuracy of the SPArc plan delivery with the gamma index of 98.3% (1%, 1mm) between reconstructed and plan doses.

Conclusion: The preliminary QA measurements and simulations demonstrate the feasibility and the accuracy of the first prototype proton arc delivery system which is complied with the clinical requirements.

PTC58-0425

Experimental assessment of inter-center variation and accuracy in SPR prediction within the European Particle Therapy Network

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Purpose/Objective: Experimental evaluation of inter-center variation and absolute accuracy in stopping-power-ratio (SPR) prediction within the European Particle Therapy Network.

Material and Methods: A head and body phantom with 17 tissue surrogate inserts were scanned consecutively at the participating centers using their individual clinical scan protocol. The SPR calculation was performed using each center's CT scan and HLUT (Fig.1). The inter-center variation and absolute accuracy in SPR prediction were quantified for lung, soft tissues and bones. To evaluate the integral effect on range prediction for typical clinical beams traversing different tissues, for three simplified beam paths the determined SPR deviations were accumulated according to their respective tissue distribution. So far, data from 12 out of 17 participating centers was analysed.

Results: A 2σ inter-center variation in SPR prediction of 7.4% and 6.1% relative to water was determined for the bone inserts in the head and body setup, respectively. Comparable results were observed for the lung tissue surrogates (5.8% and 2.8%). In the soft tissues, smaller variations were achieved (1.4% and 1.2%). For the three exemplary beam paths, inter-center variations in relative range were 2.1% on average. Moreover, absolute range deviations from reference exceeded 2% in specific centers (Fig 2B).

Conclusion: Large inter-center variations in SPR prediction were observed in low- and high-density tissue surrogates. The differences in deviation for bone between the two setups indicate a strong influence of scanning parameters such as the level of beam hardening correction, potentially resulting in range shifts of clinical relevance. Hence, inter-center standardisation is highly desirable.

PTC58-0459

Full-scale clinical prompt gamma-ray spectroscopy system for proton range verification with robotic positioning

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The prompt gamma-ray spectroscopy method for real-time range verification of proton pencil-beams has been under development at the Massachusetts General Hospital for several years. We have now completed a full-scale prototype detection system for use in our gantry treatment rooms, which is mounted on a mobile positioning robot. This system will be used for clinical studies.

The detector consists of an array of large $LaBr_3$ scintillators, mounted behind a tungsten collimator in a cylindrical rotating frame. Recent phantom experiments showed a range verification precision of 1.1 mm at a 95% confidence level for a dose of 0.9 Gy, when analyzing pencil-beams within a cylindrical volume with a radius and depth of 10 mm. Also, the elemental composition of the tissue can be determined at each pencil-beam location.

For a full assessment of the range accuracy in the upcoming clinical studies, the accuracy of the alignment of the detector with the patient is essential. We have therefore integrated the detector with a 6-axis robotic positioner. The robot is first aligned with the treatment room isocenter and then moved to a beam specific measurement position. In our initial clinical study with brain tumor patients, the system will be positioned superior of the patient. Figure 1 shows the complete system in the gantry treatment room.

We will present our first experiences with the clinical system, including the end-to-end testing in phantoms and depending on patient recruitment, the first *in vivo* measurements during clinical beam delivery.

PTC58-0467

Helium-beam radiography based on thin silicon pixel detectors: Pros and cons of the unique detection system

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To fully exploit the potential of high conformal doses of ion-beam radiotherapy, an accurate determination of the patient's *s*topping *p*ower distribution *r*elative to water (*RSP*) is particularly important, minimising range uncertainties as far as possible. In this respect, performing ion-beam radiography (iRAD) right before treatment is attractive due to the potential of direct measurements of the integrated RSP of the patient along beam direction, also called water-equivalent thickness (WET). The measured WET could be used to verify agreement between the actual RSP distribution and the one planned on.

We built a prototype detection system exclusively based on silicon pixel detectors to experimentally assess the capabilities of helium-beam radiography(αRAD). The imaging technique is based on precise energy deposition measurements of single particles in thin silicon detectors (300μm). Furthermore, a method of ion identification for the efficient suppression of background radiation and a system for ion tracking were implemented that led to significant improvements concerning the contrast-to-noise ratio and the spatial resolution of the αRads, respectively. WET differences of 0.6% could be resolved in head-sized phantoms at doses clinically applied for diagnostic x-ray radiographs, and spatial resolutions of σ_Line-SpreadFunction=1.1mm could be achieved.

In this contribution, the image quality of αRads is compared to the quality of proton-beam radiographs(pRads) obtained with the same detection system. Furthermore, the pros and cons of the unique method of energy deposition measurements in a thin silicon layer–in contrast to more common residual range/energy measurements–are discussed.

Clinics: GI, GU, Breast
PTC58-0288

Initial clinical outcomes for prostate cancer patients undergoing adjuvant or salvage post-prostatectomy proton therapy

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Purpose: To report the clinical outcomes associated with post-prostatectomy proton therapy (PT). Toxicity outcomes for this cohort were recently published.

Methods: The first 100 consecutive patients from 2010-2016 were retrospectively assessed. Biochemical failure (BF; 2 consecutive rises above the nadir), first site of clinical failure – local, regional, and/or distant metastasis (DM) – and overall survival were recorded from start of radiation. BF- and DM-free survival Kaplan-Meier curves were estimated.

Results: Median age and months after surgery were respectively 64 years (range 42-77) and 25 (5–216). PT received was 70.2 Gy (RBE) (89%), salvage (93%), prostate bed only (80%), pencil beam scanning (86%), with intensity-modulated radiation therapy (31%), and with androgen deprivation (34%). Median follow-up was 55 mo (16–80). BF was noted in 39 patients (39%). Median time to BF was 23 mo (5–69). For patients with BF, local failure was eventually noted in 1 (1%) patient at 30 mo. Regional pelvic nodal failure was noted in 4 patients (4%) – all treated to prostate bed only – at median 32 mo (10–38), 2 of whom also had DM. DM occurred in 6 patients (6%) at median 30 mo (10–41), 5 with bony and 1with lung involvement. There was 1 death at 24 mo, unrelated to prostate cancer. In summary, 4.5 yr BF free-, DM free-, and overall-survival were 61%, 94%, and 99%, respectively, in this single institution cohort treated primarily to the prostate bed only without androgen deprivation.

Conclusions: Post-prostatectomy PT is feasible with comparable clinical outcomes to historical photon outcomes.

PTC58-0239

Subsequent primary cancers after carbon ion radiotherapy, photon radiotherapy, or surgery for prostate cancer: A propensity score-weighted, retrospective, cohort study

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Background: Radiotherapy increases the risk of subsequent primary cancers. Carbon ion radiotherapy has a theoretically lower risk of inducing malignancy compared to photon, but the risk has not been analyzed yet.

Methods: We reviewed the records of patients who received carbon ion radiotherapy for prostate cancer between 1994 and 2012 at the National Institute of Radiological Sciences in Japan and compared the incidence of subsequent cancers in patients with prostate cancer treated with carbon beams to that of patients treated with photons or surgery from the Osaka Cancer Registry.

Findings: One thousand, four hundred fifty-five (1,455) patients who received carbon radiotherapy for prostate cancer met the eligibility criteria. Age and smoking were associated with a higher risk of subsequent primary cancers. One thousand, nine hundred eighty-three (1,983) patients treated with photon radiotherapy and 5,948 treated with surgery were included from the Osaka cancer registry. After propensity score weighting, carbon ion radiotherapy was associated with a lower risk of subsequent primary cancers than photon radiotherapy (hazard ratio [HR] 0·81; 95% confidence interval [CI] 0·66-0·99), while photon radiotherapy was associated with a higher risk of subsequent primary cancers than surgery (HR 1·18; 95% CI 1·02-1·36).

Interpretation: Carbon ion radiotherapy appears to have a lower risk of subsequent primary cancers than photon radiotherapy for patients with prostate cancer. Although prospective evaluation with longer follow-up is warranted to support these results, our data suggest a unique advantage of carbon ion radiotherapy and could support a wider but still cost-conscious adoption of this treatment in patients with expected long-term survival.

PTC58-0693

Colonoscopy with cauterization should be used sparingly following proton beam treatment of localized prostate cancer

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Background: Rectal toxicity, including rectal bleeding, can occur following proton beam therapy for prostate cancer. Because of the nature and location of the proton fields, this is almost always in a localized area, and may improve without cauterization.

Methods: We treated 952 patients at a single institution using proton beam therapy for definitive treatment of localized prostate cancer. All patients were on a prospective multi-institutional trial (PCG Registry), which tracked patient report outcomes and physician assessment of adverse events. Our policy was for all patients to have colonoscopy within 2 years prior to starting treatment.

Results: Nine hundred fifty-two (952) patients were treated from 10/10 through 2/17, with median follow-up of 53 months, minimum of 18 months. 147 patients with > grade 1 GI toxicity had colonoscopy following treatment. One patient was found to have colon cancer (above the treated area) 2 years after protons. Fifty-three (53) patients had cautery for rectal bleeding; most were not symptomatic other than the bleeding and only 3 had anemia or required transfusion. Eleven patients had worse symptoms after colonoscopy, 9 of whom had cautery during colonoscopy.

Conclusions: 1) It is important for patients to have colonoscopy prior to beginning treatment; 2) Procedures during colonoscopy should be limited unless there is substantial bleeding (i.e. with anemia or requiring transfusions), since intervention may lead to slower healing and more symptoms; and 3) It is important to discuss colonoscopy with gastroenterologist prior to the procedure, to avoid unnecessary biopsies, cauterization or other procedures.

PTC58-0515

Results of a randomized clinical trial comparing TACE and proton beam radiotherapy for hepatocellular carcinoma

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Objective: To compare survival rates, recurrence patterns, toxicity, and treatment cost in patients with hepatocellular carcinoma (HCC) treated with either trans-arterial chemoembolization (TACE) or proton beam radiotherapy (PBT).

Methods: Eligible subjects had untreated HCC meeting Milan or San Francisco transplant criteria and were randomized to TACE or PBT, 70.2Gy in 15 fractions. Subjects were followed with CT or MRI for recurrence or progression, toxicity, and post-treatment hospitalization. The primary endpoint was OS. Secondary endpoints were LC, PFS, toxicity and cost.

Results: Seventy-six (76) subjects were randomized, 40 to TACE and 36 to PBT. Median OS for TACE/PBT was 30 months with no difference between treatment groups. Median PFS for TACE vs PBT was 12 mo. vs not reached (p .002), HR 3.62, 95%CI 1.62-8.05. Local tumor control was improved with PBT (p .003) with TACE LF HR 5.64 95%CI 1.78-17.9. Days of post-treatment hospitalization within 30 days of treatment were TACE 166 and PBT 24. Total mean cost per patient for treatment and post treatment hospitalization was TACE $35,484 and PBT $25,410, representing a 28% cost savings for PBT.

Conclusion: OS was similar for TACE and PBT. PFS and local tumor control were improved with PBT compared to TACE. Patients treated with PBT had fewer courses of treatment, fewer post-treatment hospitalization days, and reduced cost of treatment compared to TACE.

PTC58-0241

Reduced acute toxicity after proton versus photon chemoradiation for anal cancer: Outcomes from the Proton Collaborative Group REG001-09 Trial

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Background: Most anal cancer (AC) patients experience acute grade 2 or higher (G2+) toxicity from definitive chemoradiation (CRT) with intensity modulated radiation therapy (IMRT). Although normal organ sparing has been shown favoring proton beam therapy (PBT) over IMRT, clinical outcomes of PBT for AC have not been published.

Methods: We evaluated outcomes of AC patients enrolled on the Proton Collaborative Group (PCG) REG001-09 trial (NCT01255748).

Results: Fifty-one (51) non-metastatic AC patients were treated across 5 institutions from 2010-2018; 64.7% received PBT while 35.3% received IMRT. PBT patients were older (median 69.5 vs. 60.5 years; $p=0.079$), more often male (48.5% vs. 11.1%; $p=0.008$), and had less advanced T stage ($p=0.063$) and N stage ($p=0.043$). There was no difference in median prescribed radiation dose (both 54 Gy in 30 fractions) or in the use of concurrent chemotherapy (most received 5-fluorouracil and mitomycin-C). PBT was typically delivered with pencil beam scanning (69.7%). Other radiation planning details or dosimetric outcomes were not available. Hematologic toxicity outcomes were not available. There was no difference in acute G2+ genitourinary (GU) toxicity, dermatitis, proctitis, or fatigue (Table 1). However, acute G2+ gastrointestinal (GI) toxicity was less common among PBT compared to IMRT patients treated on the PCG trial (36.4% vs. 61.1%; $p=0.09$) and compared to IMRT outcomes from the RTOG 0529 trial (36.4% vs. 73%; $p<0.001$).

Conclusions: PBT achieves a clinically meaningful reduction in acute GI toxicity compared to IMRT for AC patients receiving CRT. Additional studies are warranted to further characterize the safety and efficacy of PBT for AC.

PTC58-0045

An initial report of proton beam therapy in unresectable and localized cholangiocarcinoma

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Purpose/Objective(s): To evaluate the treatment outcome in patients with localized and unresectable cholangiocarcinoma treated by proton beam therapy (PBT).

Materials and Methods: Thirty consecutive patients with $T_{1-4}N_{0-1}M_0$ cholangiocarcinoma were included. Abdominal compression, 4-D CT and MRI simulation were routinely used. Either 66 CGE/10 fx for tumors not close to portal hepatis or bowel, or 72.6 CGE/22 fx was employed.

Results: The distribution of intrahepatic, extrahepatic, and gallbladder locations was 18 (60%), 9 (30%), and 3 (10%), respectively. The median tumor size was 7.0 cm (range: 3.4-17.5). The distribution of stage I, II, III, IV was 7%, 7%, 23% and 63%. Regional lymph node metastasis was found in 57 %. The 1-year overall survival (OS) rate was 79% and median survival time was 18 months. Seventeen (57 %) patients developed disease progression. The failure site in in-field, intrahepatic out-field and distant metastasis was 7%, 17% and 33%, respectively. The 1-year local control and progression-free survival rates were 83 % and 44%. There was no difference in local control and overall survival for N(+) and N(-) patients; however, distant metastasis was dominant failure site for N(+) patients. Among the 25 patients with biliary tract obstruction, 13 patients were free from obstructive jaundice and the median jaundice-free time was 12 months. Grade 3-4 GI toxicities happened in 10% patients.

Conclusion: Patients with unresectable and localized cholangiocarcinoma and treated by hypofractionated PBT had good local control rate and acceptable toxicities to N(+) and N(-) patients . The obstructive symptoms could be effectively relieved with sustainable duration.

PTC58-0114

Postmastectomy intensity modulated proton therapy (IMPT) after immediate breast reconstruction (IBR): Initial report of reconstruction outcomes and predictors of complications

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Purpose: The impact of proton therapy on breast reconstruction is not known. Our purpose is to report reconstructive outcomes of patients treated with IMPT following IBR.

Methods: Consecutive women with breast cancer who underwent implant-based IBR and post-mastectomy IMPT were included. Patient and treatment characteristics, dosimetry, and acute toxicity were collected prospectively and reconstruction complications retrospectively.

Results: Fifty-one (51) women received unilateral IMPT between 2015-2017, including 42 with bilateral reconstruction. Therefore, outcomes of ninety-three reconstructions were evaluable. IBR was prepectoral in 40 (78%) and subpectoral in 11 (22%). Conventional fractionation (median 50 Gy/25 fractions) was administered in 37 (73%) and hypofractionation (median 40.5 Gy/15 fractions) in 14 (27%) patients. Median mean heart, ipsilateral lung V20Gy, and CTV-IMN V95% were 0.6 Gy, 13.9%, and 97.4%. Median follow-up was 19 months. Median interval between IMPT and implant exchange was 211 days (IQR 185-267 days). Acute radiation dermatitis grade was 1 (63%), 2 (33%), and 3 (4%). Reconstruction failure (RF) occurred in 8/51 (16%) irradiated and 1/42 (2%) non-irradiated breasts (HR 7.12, p=0.032, Figure). Surgical site infection (HR 8.82, p=0.012) and unplanned surgical intervention (HR 9.86, p=0.0068) were also more common in irradiated breasts. Among irradiated breasts, hypofractionation was significantly associated with RF, as was older patient age (Table).

Conclusions: IMPT following IBR spares normal tissue and is associated with favorable acute toxicity. Reconstruction complication and failure is more common in irradiated breasts, however, outcomes compare favorably with photon literature. Hypofractionation had higher RF rates. Further investigation of optimal dose-fractionation after IBR is needed.

PTC58-0237

Reconstructive outcomes after proton beam radiation for breast cancer: A prospective cohort study

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Background: Increasing numbers of women are receiving postmastectomy radiation (PMRT) with proton beam therapy (PBT), but prospective data is lacking regarding the impact of PBT on breast reconstruction.

Materials and Methods: We conducted a prospective phase II study of non-metastatic breast cancer patients receiving PMRT with PBT from 2011-2016. Herein, we report the reconstructive outcomes of this cohort.

Results: 53/69(77%) patients underwent breast reconstruction; 23 passively scattered protons (3D-CPT), 30 pencil beam scanning (PBS). The chest wall target included the pectoralis muscles, breast prosthesis, and overlying skin. Median of mean chest wall dose was 49.9Gy (RBE) (range 44.9-51.5). 39/53(74%) underwent immediate implant-based reconstruction. Of these, 1 patient experienced implant loss before PBT and 12/38(32%) experienced complications after PBT. 3/12 experienced implant loss (1 was unrelated to PBT), 9/12 required revisions for asymmetry/contracture. 11 underwent tissue expander-to-implant exchange prior to PBT, 1 experienced implant loss before PBT and 3/11(27%) required revision for asymmetry/contracture. 3 patients did not undergo reconstruction pre-PBT, but pursued successful reconstruction afterward. Therefore, with a median follow-up of 55 months (range 17-82), 15/53(28%) experienced a PBT-related complication, and 2/53(4%) experienced reconstructive loss attributable to PBT. Among 48 patients at risk for pre-PBT implant loss, the actuarial rate of surgical re-intervention was 33% at 5 years; (24% 3D-CPT / 33% PBS, p=0.280).

Conclusions: The rate of any reconstructive complication after PBT appears consistent with those observed with conventional PMRT and true reconstruction failures are rare. Additional modifications to PBT target volumes and dose constraints may further decrease complications.

PTC58-0139

Early outcomes of hypofractionated whole breast proton beam radiotherapy with intensity modulated pencil beam scanning

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Clinical evidence supports the safety and effectiveness of hypofractionated whole breast x-ray radiotherapy in patients with early stage breast cancer with cosmetic outcomes comparable to those reported with conventional fractionation. Until recently proton use has been restricted in treating the whole breast due to the high skin entrance dose with passive scattered or uniform scanning techniques. However, protons delivered using intensity modulated pencil beam scanning (PBS) allows for proximal shaping, which controls entrance dose and provides skin sparing. The feasibility of this technique in treating the whole breast has been previously reported. The current analysis is of the first cohort of patients so treated.

34 patients were treated with hypofractionated whole breast proton radiotherapy utilizing intensity modulated PBS. Minimum time from treatment completion is 2 years. The prescribed dose was 42.72 CGE in 16 fractions to the breast followed by a tumor bed boost of 10.00 CGE in 4 fractions. Skin dose for the first 5 mm was kept between 90 and 95% of the prescription dose. All patients completed treatment without interruption. 27 patients developed grade 1 acute radiodermatitis and 7 patients grade 2. Late effects evaluated include skin and subcutaneous tissue morbidity and cosmetic score with the following findings: Grade 1 skin changes (29%), Grade 1 subcutaneous tissue (38%), Grade 2 subcutaneous tissue (3%), and cosmetic score: Good-Excellent (71%), Fair (23%) and Poor (6%). There have been no local recurrences; 2 patients died of unrelated causes.

This study suggests early outcomes comparable to those reported for x-ray therapy.

Clinics: Pediatric
PTC58-0312

Risk of radiation-induced cerebral vasculopathy in pediatric patients treated with proton radiotherapy for brain tumors

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Background/Purpose: Progressive narrowing of the large cerebral vessels, also referred to as radiation-induced cerebral vasculopathy (RICV) or moyamoya-like disease can develop in pediatric patients treated with radiotherapy (RT) for brain tumors. Risk factors associated with RICV are not well elucidated. Here we report the association between radiation dose to the circle of Willis (CW) and vasculopathy in a cohort of pediatric patients treated with proton radiotherapy (PRT).

Methods: We retrospectively reviewed patients <22 years with brain tumors treated with PRT at Massachusetts General Hospital between January 2001 and September 2018. Patients were eligible if they had one year of follow up post-RT and had tumors in the suprasellar, hypothalamic, or posterior fossa regions. We collected demographic and clinical variables (Table 1) and analyzed dosimetry data, including maximum (Dmax) and mean dose to the CW.

Results: Of 622 patients who met eligibility criteria, 14 (2.3%) developed RICV after PBT. The median follow-up was 6.3 years (range:1.28-21.2) and median time to development of RICV was 1.8 years (range: 0.9-7.3). The most common diagnoses in patients with RICV were craniopharyngioma (36%) and low-grade gliomas (29%). All patients who developed RICV received a Dmax >50 Gy to the CW. Stenosis occurred most commonly in the supraclinoid internal carotid and the middle and anterior cerebral arteries.

Conclusions: Pediatric brain tumor survivors remain at risk for developing RICV years after completion of PRT. Dose >50 Gy to the circle of Willis is an important risk factor for RICV and warrants further investigation.

PTC58-0703

Beware of pseudoprogression in group III pelvic rhabdomyosarcoma patients undergoing proton therapy for bladder preservation

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Purpose: Report the incidence and consequence of pseudoprogression following proton therapy for unresectable pelvic rhabdomyosarcoma.

Methods: We reviewed the medical records of 17 children (≤21 years old) with unresectable group III pelvic rhabdomyosarcoma enrolled on a prospective outcome study and treated between 2007 and 2018. The median age was 3.1 years old. Fifteen of 17 patients were male and 15/17 had embryonal RMS, including 3 botryoid subtype. At diagnosis, the median tumor volume was 218 cc and the median maximum diameter was 9.4 cm. Two patients had N1 disease. Seven and 10 patients received EpSSG- and COG- based chemotherapy, respectively. The median radiation dose was 50.4 CGE.

Results: With a median follow-up of 3.3 years, the 5-year local control (LC), progression free (PFS), and overall survival (OS) is 79%, 71%, and 79% respectively. Overall, 14/15 survivors retain a functional bladder. Seven patients who had pseudoprogression, characterized by persistent tumor mass or thickened bladder wall, underwent additional diagnostic surgery at a median of 7 months (range 2-24 months) following proton therapy. Procedures included 6 biopsies and 1 partial cystectomy. Pathology revealed mature rhabdomyoblasts or cystitis cystica. Postoperatively, 4/7 experienced grade 3 bladder toxicity, including prolonged hematuria, cystitis, and dysuria. Two of the 6 who underwent biopsy have nocturnal enuresis at age 7 and 9, compared to 0/11 in the non-pseudoprogression cohort.

Conclusion: In children undergoing proton therapy for unresectable pelvic rhabdomyosarcoma, pseudoprogression is common and unnecessary intervention may result in more bladder toxicity than chemoradiotherapy itself.

PTC58-0707

Outcomes following proton therapy for group III pelvic rhabdomyosarcoma

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Purpose: Report institutional outcomes following proton therapy for pelvic rhabdomyosarcoma (RMS).

Methods: Thirty-one (31) consecutive children (≤21 years old) with group III pelvic rhabdomyosarcoma were enrolled on a prospective outcome study and treated between 2007 and 2018. Vaginal/cervical RMS patients were excluded. The median age was 2.6 years old. Twenty-four patients had embryonal RMS. At diagnosis, the median tumor volume was 185 cc and the median maximum diameter was 9.4 cm. Seven patients had N1 disease. Nineteen and 12 patients received EpSSG- and COG- based chemotherapy, respectively. Fourteen patients underwent resection of the primary tumor following induction chemotherapy, including 6 who had total cystectomy. The median radiation dose was 50.4 CGE.

Results: With a median follow-up of 3.8 years, the 5-year local control (LC), progression free (PFS), and overall survival (OS) is 86%, 82%, and 90%, respectively. Patients < 3 years old had significantly improved local control (100% vs 72%, $p = 0.04$). No other factors were significantly associated with disease control or survival. Specifically, there was no statistically significant difference observed in LC, PFS, or OS when comparing patients who underwent biopsy vs gross total resection (79% vs 93%, 71% vs 93%, 79% vs 100%, respectively). Excluding patients who underwent cystectomy, urinary toxicity is limited to three patients with nocturnal enuresis and one patient with intermittent urinary retention.

Conclusion: This cohort of young children with large pelvic tumors treated with proton therapy demonstrate similar local control with less toxicity than historic reports. Functional bladder preservation is possible in most patients.

PTC58-0087

Variations and dosimetric impact of bowel gas volume due to general anesthesia with pencil-beam-scanning-proton-beam-therapy versus intensity-modulated radiotherapy in paediatric abdominal neuroblastoma

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Background: General anesthesia (GA) is occasionally used for immobilisation during paediatric radiotherapy. This work investigates the impact of GA on variations in bowel air and the dosimetric implications on Pencil-Beam-Scanning Proton-Beam-Therapy (PBS-PBT) versus Intensity-Modulated-Radiotherapy (IMRT).

Methods: Forty-three (43) weekly Cone-beam-Computed-Tomography (CBCT) from 11 patients treated with abdominal radiotherapy for high-risk neuroblastoma were used to evaluate bowel air variations. 5 received 21Gy/14f/3-weeks and 6 received 36Gy/24f/5-weeks. Twenty (20) plans from an in-house PBS-PBT vs IMRT double-planning study were used to analyse the dosimetric impact of bowel air variations. Dose re-calculations were done after bowel volume was substituted with air (HU-700) and water (HU0). The difference to the respective nominal plan for target volume D98%, D95%, D50%, D5% and D2% coverage was calculated.

Results: The mean variation in the percentage of air within the bowel and bowel-PTV-overlap volume was significantly larger in the GA(n=6) vs non-GA cohort(n=5), 40% vs 12.6%(p=0.004) and 34.9% vs 5.2%(p=0.004). There was no significant correlation between radiotherapy course, bowel volume, bowel-PTV-overlap volume with the degree of bowel air variation. When bowel was filled with air, D98% and D95% for PBS-PBT was significantly reduced vs IMRT(median -16.3% vs +0.5%;p=0.002 and -11.8% vs +0.5%;p=0.000). When bowel was filled with water, D50%, D5% and D2% was slightly increased for PBS-PBT vs IMRT (median +1.8% vs 0%;p=0.001, +1.95% vs 0%;p=0.005 and +2.55% vs -0.5%;p=0.004).

Conclusion: Variations in bowel air was greatest in the GA cohort, with an increase resulting in target volume under-dosage with PBS-PBT. This must be taken into consideration when selecting the optimal radiation modality for abdominal neuroblastoma.

PTC58-0463

First application of voxel-based analysis for robust identification of brain MRI changes following proton therapy of pediatric CNS tumors

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Background: Proton therapy (PT) is increasingly used to treat pediatric brain tumors. Unanticipated normal brain tissue changes observed in magnetic resonance imaging (MRI) has spurred discussions about the relative biological effectiveness of PT. Identification of brain changes in pediatric patients is challenged by the continuous growth, external factors (e.g. surgery), and tumor response. The aim of this work was to explore the feasibility of a voxel-based method adapted from the neuroscience field to identify longitudinal MRI changes following PT and photon-based radiotherapy (RT) for pediatric brain tumors.

Materials and Method: Six patients (8.5 [4.2,13.5] years old at treatment) with brain tumors treated with either PT (N=4) or photon-based RT (N=2) were included. All patients had pretreatment MRI and subsequent follow-up MRI (on the same scanner and with the same sequences) every six months after treatment, with 4-10 scans per patient (follow-up time 2.2-4.9 years).

For each patient the average brain template was created using the available MRI scans. Then, each MRI was registered to the average template and change over time in cortical thickness (CTh) and T1 relaxation time was evaluated at each cortex point of the whole brain (Fig. 1).

Results: The CTh decreased during the follow-up for three of the patients (0.004-0.021mm/year; $p<0.01$), while T1 increased for two patients (0.02-0.07ms/year; $p<0.05$, Fig. 2).

Conclusion: Our method can identify subtle changes in brain substructures following PT/RT for CNS tumors in pediatric patients. In future studies we will differentiate radiation-induced alterations from normal growth and/or non-treatment related changes.

PTC58-0688

Combined approach for craniopharyngioma in children with conservative surgery and proton therapy: A phase II study for dose escalation evaluation

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Conservative surgery and radiation therapy, particularly when hypothalamic infiltration, tend to be a consensus. Proton therapy (PT) offers further sparing of normal tissues compared to photons. The objectives of this study were; To assess efficacy of limited surgery followed by PT in children with craniopharyngioma; To evaluate feasibility of dose escalation while maintaining risk-adapted dose constraints to the chiasm.

33 patients were included (17 males), median age 9.0 years (2.1-15.5) at diagnosis, 9.6 years (3.3-15.8) at PT. All patients underwent surgical approach (1-5, median 2) with measurable residue. Median interval from diagnosis was 7.2 months (2.5-73.6); Median PTV 31.1 cm3 (12.7-136). Imaging during PT showed increased cystic component volume in 11 patients, 2 requiring re-planning. Median dose was 54.4CGE (52.2-56.1). Based on dosimetric parameters, 5 patients underwent moderate dose escalation. The chiasm received 52.7CGE median dose (51.8-54.4).

At median follow-up 4.3 years (1.3-7.0) since radiation, 32 patients are alive. Three patients relapsed 2 locally 1 metastatic. 25/32 patients have normal vision in at least one eye, 17/32 have restricted fields. All patients are on hormone replacement. Median BMI is 24.1 (18.7-36.3) with 11 patients overweight and 9 obese. 24 patients have normal academic status, 8 patients require special schooling.

This study supports the use of proton therapy in pediatric craniopharyngioma. The secondary objective of dose escalation using passive scattering delivery could be reached in few patients only. Intensity modulated proton therapy might help further examining dose effect relationship.

Clinics: CNS / Skull Base
PTC58-0251

Particle radiation therapy in the management of malignant glioma: Experience at the Shanghai Proton and Heavy Ion Center

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Purpose: To evaluate the outcomes of patients with high-grade glioma (HGG) treated with particle radiotherapy (proton +/- carbon-ion radiotherapy [CIRT]).

Methods: Between 6/2015 and 10/2018, 50 consecutive and non-selected patients with glioblastoma multiforme (n=34), anaplastic glioma (n=16) were treated at the Shanghai Proton and Heavy Ion Center. Twenty-four patients received proton (60GyE/30 daily fractions), and 26 patients had proton plus CIRT boost in various dose-escalating trials (doses $\geq$ 60GyE in all cases). The characteristics of patients, their conditions, and treatments were detailed in the Table. Progression-free (PFS) and overall survival (OS) rates, as well as treatment-induced toxicities were analyzed.

Results: With a median follow-up time of 14.3 (range 4.8-39.6) months, the 12- and 18-month OS rates were 87.8% and 72.8%, and those of the PFS were 74.2% and 59.8%, respectively for the entire cohort (Figure). Univariate analyses revealed that age ($>$ vs. $\leq$ 50), WHO grade (III vs. IV), and performance status (KPS $>$ vs. $\leq$ 80) were significant prognosticators for OS; IDH mutation and WHO grade were significant for predicting PFS (Figure). Furthermore, MGMT promoter methylation, performance status, and age showed a trend to predict PFS. No significant predictive factors for PFS or OS were found in multivariate analyses. Twenty-nine patients developed grade 1 dermatitis/alopecia, 11 developed pseudoprogression subsequently subsided or confirmed by pathology, and 11 developed grade 1-2 radiation necrosis. No grade 3-5 toxicities were observed.

Conclusions: Particle radiotherapy produced an 18-month OS and PFS rates of 72.8% and 59.8% with acceptable adverse-effects in patients with HGG.

PTC58-0198

Proton therapy in the treatment of low-grade gliomas

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Background: Proton therapy (PT) has the potential to achieve long term local control with reduced radiation-related toxicity in patients with low grade glioma (LGG). However, the available data is scarce. We present our preliminary analysis of outcome and toxicity.

Methods: Prospectively collected data from 71 patients with WHO°I-II intracranial non-metastatic glioma treated with PT between January 2013 and December 2017 was analyzed. The median follow-up (FU) from diagnosis and from PT was 3.9 years (range 1.0-16.7) and 1.6 years (range 0.4-4.4), respectively. Side effects were documented according to CTCAE v4.0 before, during and after PT. The overall survival (OS), progression free survival (PFS) and toxicity were analyzed. Median total dose of PT was 54 $Gy_{1.1}$ (range 50.4-59.4).

Results: Patient and tumor characteristics are shown in tab. 1. Seizures and visual problems were the most common presenting symptoms at diagnosis. Median time from diagnosis to PT was 25.64 months (range 1.3-185.2). PT was administered most commonly as second- or third-line therapy (60.5%, n=43). In the rest, it was used as part of initial therapy either postoperatively (23%, n=16), or as definitive treatment (16.5%, n=12). Median clinical target volume (CTV) was 75.2cc (range: 2.2-340.2cc). At 2 years after PT, OS (Fig.1) and PFS were 96.9% and 79.4%, respectively. No correlation was found between PFS and age, CTV volume, resection status before PT or chemotherapy. At last FU, neurological status was improved in 20% (n=14) and worsened in 7% (n=5).

Conclusions: Early results show good feasibility and high tumor control of PT in patients with LGG.

PTC58-0361

Routine neurocognitive testing of patients treated with proton therapy on a prospective registry study: Feasibility and first results

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Patients with CNS and skull base tumors treated with proton therapy undergo routine, repeat neurocognitive testing as part our Registry Study. 112 of 152 eligible patients participated. We report on feasibility, patient acceptance, and early results.

A battery of standardized EORTC tests was employed. The Hopkins Verbal Learning Test (HLTV-R) tests immediate and delayed verbal memory. Trail Making Test Part A and B (TMT-A and B) assesses concentration, processing speed and cognitive flexibility. The Controlled Oral Word Association Test (COWA) evaluates verbal fluency and executive function. The Grooved Pegboard Test evaluates visual motor coordination. Tested time points were at baseline, at treatment completion, at 3, 6,12 months and once yearly thereafter.

The first 4 time points (baseline, treatment end, at 3 and 6 months) were evaluated in 112, 94, 61 and 40 patients. Test completion rates were 99%, 96%, 98%, and 98 % at the time points. No significant differences were found in verbal memory (HVLT-R), cognitive flexibility, executive function (TMT-B) and motor coordination. Between baseline and at 6 months significant worsening was found in speed processing (TMT-A, p=.002), however, significant improvement in verbal fluency (COWA, p=.000).

First and early results on neurocognitive function testing as part of a Registry Study following proton therapy demonstrate variable changes of different neurocognitive functions. High compliance rates confirm patient acceptance and testing feasibility requiring limited staffing resources. Longer follow up and larger patient numbers will permit subgroup analyses, correlation with clinical outcomes and dose volume histogram parameters.

PTC58-0188

Predictive factors of brain necrosis in proton therapy

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Purpose*:* High-dose fractionated radiotherapy achieves long-term tumor control in several types of tumors involving or within close proximity to the brain whereas limited dose constraints are available. This study investigated the significance of the three-dimensional dose distribution of double scattering proton therapy to the brain with clinicopathological factors on the development of symptomatic radiation necrosis.

Patients and Methods*:* Patients with head and neck, cranial base, or intracranial tumors who underwent proton therapy with collateral moderate to high dose radiation exposure to the nontarget brain were retrospectively reviewed. A mixture cure model with respect to necrosis-free survival was used to derive NTCP estimates while adjusting for potential confounding factors.

Results*:* Of 179 identified patients, 83 patients had intracranial tumors and 96 patients had primary extracranial tumors. The optimal dose measure obtained to describe the occurrence of radiation necrosis was the equivalent uniform dose (EUD) with parameter a=9. The best-fit parameters of logistic NTCP models revealed D_{50}=57.7Gy for intracranial tumors, D_{50}=39.5Gy for extracranial tumors, and g_{50}=2.5 for both tumor locations. Multivariable analysis revealed EUD and primary tumor location to be the strongest predictors of brain radiation necrosis.

Conclusion*:* This is the first report using volumetric data to predict the development of radiation necrosis. Multivariable modelling identified EUD to be an independent and strong predictor for brain radiation necrosis.

PTC58-0716

Proton beam radiotherapy for patients with pituitary adenomas is associated with low acute and late treatment-related toxicities

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Objective: To report on the treatment-related toxicities associated with proton beam radiotherapy (PBT) for patients with pituitary adenomas.

Methods: Patients treated with PBT for newly diagnosed or recurrent disease were selected from a prospective multi-institutional registry. Acute and late treatment-related toxicity outcomes were measured according the CTCAE v.4.

Results: 46 patients met eligibility criteria for inclusion in this study. The median age at treatment was 53 years (Range: 21-82). 10 patients (22%) had previously received photon radiotherapy before salvage PBT. 43 patients (93%) underwent resection prior to PBT at a median of 10 months (Range: 2-238). The median dose was 50.4 Gy in 28 fractions (Range: 25.2 - 59.5 Gy in 21-60 fractions). 19 (41%) patients were treated with pencil beam scanning technique and 27 (59%) were treated with uniform scanning/passive scatter. The median follow-up from the last date of radiotherapy was 32 months (Range: 4 - 131). Of the patients with clinical and imaging follow-up, all patients had stable or controlled disease at last follow-up. Nine patients (20%) experienced an acute grade 2 toxicity and two patients (4%) experienced acute grade 3 toxicities: blurred vision and headache. Two patients (4%) experienced a grade 2 late toxicity and no grade 3 late toxicities in any domains were observed.

Conclusions: In this prospective multi-institutional study of patients treated with PBT for pituitary adenomas, few significant acute and late treatment-related toxicities were observed. Prospective neurocognitive and quality-of-life studies are needed to determine additional benefits of this treatment technique in this patient population.

PTC58-0468

Early outcomes of hearing preservation following fractionated proton radiation therapy for vestibular schwannoma

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Introduction: Vestibular schwannomas (VS) are benign tumors that can result in significant hearing loss, tinnitus and other cranial nerve deficits. Management options include definitive radiation therapy, including fractionated stereotactic radiation therapy (fSRT). We present the interim results of a prospective study of proton fSRT for the management of VS.

Methods: This is a single arm prospective study of VS patients with subjectively useful hearing in the affected ear, indicated for radiation treatment, and treated with primary outcome of hearing preservation. Requirements included tumor no greater than 3 cm and no prior radiation therapy. fSRT was 50.4-54 Gy(RBE) at 1.8 Gy(RBE) fractions. Toxicity was evaluated using NCI CTCAE v4. Comprehensive audiologic evaluation, neurological exam, and tinnitus questionnaire were conducted at baseline, 6 months following treatment and annually for 5 years. Secondary endpoints include tumor local control and treatment toxicities. Here, we report our 6 months data.

Results: Between 2011-2017, 20 patients (median age 62) were enrolled on study and completed treatment without difficulty. Fourteen patients were women, all had unilateral tumors with 11 with left-sided tumor. Median tumor size was 1.6 cm. All patients tolerated proton fSRT without difficulty. At 6 months, 42% of patients experienced a decrement in hearing loss in the irradiated ear (Table 1). Local control was 100%. The only grade 3 and 4 toxicity was hearing loss, occurring in two and one case, respectively.

Conclusion: Early results follow proton fSRT demonstrates a decrement in hearing loss in almost half of patients but all with still serviceable hearing.

PTC58-0559

Outcomes, prognostic factors, and salvage treatment for recurrent chordoma after spot-scanning proton therapy at the Paul Scherrer Institute

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Purpose*:* The outcome of patients with recurring chordoma after proton therapy (PT) is not well established. We assessed the cancer-specific (CSS) and overall survival (OS) of patients recurring after PT and evaluated the prognostic factors affecting CSS.

Methods and Materials*:* A retrospective analysis was made on 71 recurring skull base (n=36) and extracranial (n=35) chordoma patients who initially received proton therapy in the adjuvant (n=42; 59.2%) or salvage (n=29; 40.8%) setting. The median PT dose delivered was 74 (range, 62 – 76) GyRBE. Mean age was 55±14.2 years and the male/female ratio was approximately one.

Results*:* Median time to first failure after PT was 30.8 months (range, 3 – 152). Most patients (n=59; 83.1%) presented with loco-regional failure only. There were only 12 (16.9%) distant failures, either with (n=5) or without (n=7) synchronous local failure. Eight (11.3%) patients received no salvage therapy for their first progression after PT. Salvage treatments after PT failure included surgery, systemic therapy, and radiotherapy in 45 (63.2%), 20 (28.2%), and 8 (11.3%) patients, respectively. Fifty-three (74.6%) patients died, most often from uncontrolled tumor (47 of 53 patients; 88.7%). The median CSS and OS was 3.9 (95%CI 3.1 to 5.1) and 3.4 (95%CI 2.5 to 4.4) years, respectively. On multivariate analysis, extracranial location and late failure (≥30.8 months after PT) were independent favourable prognostic factors for CSS.

Conclusions*:* The survival of chordoma patients after a recurrence following PT is poor, particularly for patients who relapse early or recur in the skull base.

PTC58-0294

Skull-base chordoma treated with proton and carbon ion radiotherapy: CNAO experience

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Purpose: Evaluate local control (LC) and toxicity profiles of patients (pts) with skull-base chordoma treated with particle therapy (proton therapy -PT- and carbon ion therapy -CIRT-)

Material and Methods: Between November 2011 and June 2018, 148 pts with histologically proven skull-base chordoma were treated with particle therapy at CNAO. All but one pts had previous surgery and complete macroscopic resection was achieved only in 21 pts (14%). 77 pts were treated with CIRT, 70 with PT, one patient with mixed beam proton/carbon ion. The particle choice (proton or carbon ion) was made on personalized basis. The total dose was 70,4 Gy RBE for CIRT, and 74 Gy RBE for PT. Clinical outcomes (LC, 2-year local relapse free- LRFS and overall -survival -OS-) and toxicity profiles in according with CTCAE v4.03 were evaluated.

Results: The median follow-up was 32 months (range, 4-76 months). LC was 82%. In pts that underwent complete macroscopic surgery followed by PT, LC was 100%. The 2-year LRFS and OS were 80% and 98% respectively. In field recurrence occurred in 18% (25 pts). In 15 (60%) cases of recurrences the tumor was in close contiguity to the brainstem. Out of field recurrence/metastasis were found in 12 pts (8%). The toxicity profile was favorable. High grade (G3-G4) late toxicity occurred in 6 pts (4%).

Conclusion: Particle therapy is a safe and effective treatment among pts with skull-base chordoma.

PTC58-0132

Stereotactic proton ablative radiosurgery (SPAR) of the spine: A report on toxicity and efficacy

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Purpose: Image-guided stereotactic proton ablative radiosurgery (SPAR) is a novel approach in the management of spine metastases, especially in re-irradiation setting. We present safety and efficacy data.

Methods and Materials: Between June 2015 and July 2018, 34 patients received SPAR (1-5 fractions). One 6 Gyx10-fraction was used in multilevel spine involvement. Patients were immobilized with vac lok, indexed knee cushion, and memory foam, and treated on Hitachi PROBEAT-V with either single- or multi-field optimized intensity modulated scanning proton beam using 2D/3D kV algorithm and CT-on-rails volumetric localization per treating physician. Intra-fraction motion was monitored with VisionRT and 2D/3D kV imaging as needed. Offline plan evaluation was performed on as-needed basis. MRI, CT, and/or PET were assessed for clinical outcomes.

Results: Median age was 64 and 30% were females. 44% were prostate histology, and 82% had prior overlapping radiotherapy fields. Forty metastatic spine sites were treated [T(8), L(15), and sacrum(17)]. Median dose per fraction and number of fractions were 12.5Gy and 3. Median follow up was $>$21.8 months and 15-month OS was 69% (median not reached). 15-month local recurrence and distant metastasis were 24% and 71%. There was no Grade$\geq$3 toxicity. Grade1 toxicity was 38% with fatigue (n=7) being most common. Grade2 toxicity was 15%. Four patients experienced acute flare-up bone pain, and 2 patients with pain had worsened pain at 6 months post-SPAR. One compression fracture required vertebroplasty.

Conclusion: SPAR for spine metastases is a safe and effective treatment method especially in re-irradiation setting and should be considered in patients with oligometastasis with longer expected survival.

Clinics: Head and Neck / Eye
PTC58-0273

Carbon ion radiation therapy performed as re-irradiation in patients with locoregionally recurrent head and neck malignancies

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Purpose: To report the experience of carbon-ion radiotherapy (CIRT) in 233 previously irradiated patients with locoregionally recurrent head/neck malignancies.

Methods: Between 6/2014 and 5/2018, 233 patients were re-irradiated with CIRT using pencil beam scanning technology for locoregionally recurrent head/neck squamous cell carcinoma (n=183), adenoid cystic carcinoma (n=17), sarcomas including radiation-induced second primaries (n=17), adenocarcinoma (n=5), or other pathologies (n=11). Table 1 detailed the characteristics of patients, their conditions, and treatment regimens. Disease control and survival rates, treatment-induced toxicities, and prognostic factors were the foci of analyses.

Results: With a median follow-up of 12.0 (range 2.0-45.0) months, the 18-month overall (OS), progression-free, local-progression free (LPFS), regional-progression-free, and distant-metastasis-free survival rates were 86.3%, 59.4%, 70.7%, 93.8%, and 94.0%, respectively (Table 2, Figure 1). Two patients experienced grade 3 acute mucositis during CIRT. Severe late toxicities (grade 3/4) were infrequent, but included xerostomia (n=1, 0.4%), temporal lobe injury (n=1, 0.4%), and mucosal necrosis (n=28, 12.0%) including 16 patients with hemorrhage (6.9%). Ten (4.3%) patients died of hemorrhage with or without evidence of local progression after CIRT. Multivariate analyses revealed second primary sarcoma was a significant negative prognosticator for OS (Table 3); Higher CIRT dose fraction size showed a trend for improving LPFS (Table 4).

Conclusion: CIRT offers an effective salvage modality for locoregionally recurrent head/neck malignancies after previous radiotherapy. Adverse effects and 18-month disease control and survival rates to CIRT were favorable. Further follow-up is needed to evaluate the long-term outcomes.

PTC58-0280

Estimating individual quality of life benefit and cost effectiveness of proton therapy for patients with oropharyngeal head and neck cancer

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Purpose/Objective: Using a quantitative decision-support system we estimated the normal tissue complication (NTC) quality of life burden after definitive RT for oropharyngeal cancer (OPC), comparing photon and proton RT.

Material/Methods: NTC probability for dysphagia, esophagitis, hypothyroidism, xerostomia and oral mucositis was estimated for 33 OPC patients, comparing delivered photon IMRT plans and intensity-modulated proton therapy (IMPT) plans generated using clinical protocols at a collaborating PT center. Plans had equivalent target coverage and robustness optimization was used for IMPT plans. Latencies and durations of NTCs were modeled while accounting for disease-specific age-, sex-, and smoking status-adjusted conditional survival probability. The quality-adjusted life years (QALYs) lost attributable to each NTC were calculated by assigning quality-adjustment factors based on complication severity. Cost effectiveness was modeled based on the upfront cost of IMPT ($36,659) and IMRT ($20,257), and interventions related to NTCs, with 3%/year discounting of QALYs and long-term costs.

Results: The average QALYs lost from all NTCs were 1.52y and 1.15y for IMRT and IMPT, respectively, with average 0.37y spared with IMPT (95% CI: 0.27y-2.53y). The QALYs spared with proton RT varied considerably between patients, from 0.06 to 0.84 QALYs. Younger patients with p16-positive tumors and $\leq$10 pack-years smoked had the greatest benefit (Figure1). IMPT cost effectiveness varied greatly between patients (Table1).

Conclusion: Using this decision-support tool we identified patients for which IMPT is estimated to have the greatest benefit and would be most cost effective. This can help optimize resource allocation and patient selection for trials aimed at improving quality of life.

PTC58-0365

Clinical outcomes of particle radiotherapy for head and neck sarcomas

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Purpose: To report the outcomes of patients with head and neck sarcomas (HNS) treated with particle (proton/carbon-ion) radiotherapy (PRT).

Patients and Methods: Between 7/2014 and 11/2018, 73 consecutive and non-selected patients with HNS were treated with PRT at the Shanghai Proton and Heavy Ion Center. The characteristics of patients, their conditions, and treatments were detailed in Table 1. Kaplan-Meier estimator was used to calculate overall survival (OS), local relapse-free survival (LRFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS). The Cox proportional hazard method was performed to determine independent prognostic factors. CTCAE 4.03 was used to evaluate toxicities.

Results: With median follow-up time of 15.7 (range 2.4-91.7) months, the 18-month OS, LRFS, DMFS, and PFS rates were 90.0%, 80.1%, 83.3%, and 63.6%, respectively, for the entire cohort of 73 patients. Five of 18 previously irradiated patients deceased after salvage carbon-ion radiotherapy. For the remaining 55 radiation-naïve patients, the 18-month OS, LRFS, DMFS, and PFS after PRT were 100.0%, 84.9%, 84.8%, and 70.3%, respectively. Grade 1∼2 acute side effects were observed in 30 patients (41.1%) and 39 patients (53.5%) remained intact. Three patients (4.1%) experienced acute mucositis in the oral cavity and oropharynx. One patient (1.3%) experienced grade 4 hemorrhage. Multivariate analyses revealed that re-irradiation was an independent predictive factor for PFS ($p=0.015$) with hazard ratio of 6.24 (Table 2).

Conclusion: PRT provided favorable local control and overall survival rates with few severe acute/late toxicities for patients with HNS. Distant metastasis is the main mode of treatment failure.

PTC58-0477

Intensity-modulated proton therapy reduce acute toxicity for non-NPC head and neck cancer, a propensity score matching study

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Purpose: To evaluate treatment outcomes and toxicity profiles of Intensity-Modulated Proton Therapy (IMPT) in non-NPC head and neck cancer patients.

Material and Methods: We retrieved non-NPC head and neck cancer patients treated from 2016 to July-2018 and excluded the following: palliative intent treatment or benign disease, having re-RT history, non-squamous histology. Stage, age, gender, disease location, operation history, concurrent chemotherapy, smoking and HPV status were used for propensity score matching (PSM). The photon therapy group was treated by RapidArc. The proton group was treated by IMPT. Multi-field optimization was used in IMPT planning. The treatment toxicity was recorded according to CTCAEv.4.0.

Results: After PSM, there were 68 patients in each group. Proton group had better 1-year-OS(92.3% V.S. 82.4%, p=0.217). There were no significant difference in 1-year LC(92.1% V.S 91.5%, p=0.686), RC(89.6% V.S. 86.8%, p=0.926) and DMF(96.4% V.S. 93.1%, p=0.466). 36.8% patient need tube feeding during treatment in proton group, which is lower than 59.7%(p=0.058) in photon patients. Tube dependent rate was also lower in proton group (5.9% V.S. 11.8%, p=0.365). Besides, weight loss during acute phase was lower in proton group (-4.4% V.S. -6.0%, p=0.045). Patients in proton group also had less >grade 3 hematologic toxicities (neutropenia 3.3% V.S. 7.3%, p=0.421; lymphopenia 50.8% V.S. 78.2%, p=0.003). More patients needed admission during treatment in photon group (38.2% V.S. 19.1%, p=0.022).

Conclusion: Although the current study is retrospective, this is the first report about IMPT for head and neck cancer including patients with oral cavity, hypopharynx and larynx cancer. Compared to photon therapy, IMPT results in a favorable OS and reduces weight loss, tube feeding and hematologic toxicity.

PTC58-0335

Particle radiotherapy in the management of adenoid cystic carcinoma: Experience at the Shanghai Proton and Heavy Ion Center (SPHIC)

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Purpose: To evaluate the outcomes of patients with adenoid cystic carcinoma (ACC) treated with particle radiotherapy (carbon-ion radiotherapy [CIRT] and proton therapy).

Methods: Between 6/2015 and 11/2018, 108 consecutive and non-selected (including 17 previously irradiated) patients were treated with particle radiotherapy at the SPHIC. The characteristics of patients, their conditions, and treatments were detailed in Table 1. Disease control, survival, and treatment-induced toxicities were the foci of the current analyses. Kaplan-Meier estimator was used to calculate disease control and survival time.

Results: With a median follow-up time of 18.0 (range 3.0-60.0) months, only 1 patient who completed salvage CIRT for local recurrent ACC died. The 18-month overall (OS), progression-free (PFS), locoregional progression-free (LPFS), and distant metastasis-free (DMFS) survival rates were 98.9%, 83.5%, 95.4%, and 89.8%, respectively (Figure). Univariate analyses using Cox regression revealed that tumor site (oropharynx for PFS; oropharynx and skull base for DMFS) were significant prognostic factors (Table 2–4). No other significant prognosticators were observed in both uni- and multi-variate analyses due to lack of events.

Acute/late grade 2 xerostomia were seen in 8 and 5 patients, respectively. Additionally, 1 patient had grade 2 hypoglossal nerve palsy and another experienced grade 2 visual impairment as late toxicity. No toxicity of $\geq$ grade 3 was observed.

Conclusions: Particle radiotherapy produced favorable outcomes in terms of 18-month OS, PFS, and LPFS rates (98.9%, 83.5%, and 95.4%) for ACC with moderate toxicities. Such outcomes will be confirmed in an ongoing prospective trial at SPHIC.

PTC58-0424

Reirradiation of salivary gland tumors with carbon ion radiotherapy (CIRT) at CNAO

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Purpose: To report oncologic and functional outcomes of carbon ion radiotherapy (CIRT) in re-radiation setting for recurrent salivary gland tumors at CNAO.

Methods: From November 2013 to December 2016 patients (pts) with recurrent salivary gland tumors were enrolled in a phase-II protocol (CNAO-S14) to evaluate outcome of CIRT in the setting of re-radiation in terms of toxicity and tumor control.

Results: A total of 51 pts met the criteria of the study. Majority of pts (74.5%) had adenoid cystic carcinoma, rcT4a (51%) and rcT4b (37%). Median dose of prior photon-based radiation was 60 Gy. Median dose of CIRT at the time of re-radiation was 60 GyE at 3 GyE per fraction. During re-radiation, 11 pts (21.6%) had G0 toxicity, 19 pts (37.3%) had G1, 19 pts (37.3%) had G2 and 2 pts (3.9%) had G3. Median Follow-up was 19 months. Twenty-one (41.2%) pts had stable disease and 30 pts (58.8%) tumor progression at the time of last follow up. Furthermore, 14 pts (27.5%) had no late toxicity, 9 (18%) pts had G1, 19 pts (37%) had G2 and 9 pts (17. 5%) had G3. Using Kaplan Meier method, estimated progression free survival PFS (actuarial) at one, two and three years were 80%, 65.1% and 43.5% respectively. Estimated overall survival OS (actuarial) at one, two and three years were 90.2%, 69.1% and 54.5% respectively.

Conclusions: In a re-radiation setting, CIRT is effective in controlling local progression of recurrent salivary gland tumors along with acceptable rates of acute and late toxicity.

PTC58-0539

A comparison of health-related quality of life in head and neck cancer patients between proton and photon radiotherapy

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Background: We hypothesized that patients with head and neck cancer treated with Intensity Modulated Proton Therapy (IMPT) would have a better health-related quality of life (HRQoL) compared to those who received Volumetric Modulated Arc Therapy (VMAT).

Materials and Methods: From 2016 to 2018, patient-reported outcome data utilizing Functional Assessment of Cancer Therapy-Head & Neck Cancer (FACT-H&N) from patients treated with radiotherapy (RT) for head and neck cancer were collected. Patients with palliative intent treatment, previous RT, nasopharyngeal cancer, and non-squamous cell carcinoma histology were excluded. Propensity Score Matching (PSM) with 1:1 ratio was used for matching the IMPT group with the VMAT group. The differences between pretreatment scores and scores at various time points (during RT, post-RT 3 months, 6 months, and 1 year) were calculated and compared between two groups.

Results: After PSM, results from 38 patients in each group were analyzed. The reduction of Functional Assessment of Cancer Therapy-General (FACT-G) score of VMAT group was significantly larger than IMPT group at 6 months and 1 year after the RT (-4.88 vs 4.04, $p=0.04$; -5.08 vs. 4.89, $p=0.023$, respectively). The reduction of FACT-H&N score was also significantly larger in VMAT group (-8.06 vs. 4.84, $p=0.02$) at the time point of one year after the RT. There was no statistical difference between the two groups in the consisting domains.

Conclusion: IMPT technique provides better HRQoL to the head and neck cancer patients who receive RT.

PTC58-0096

Circumscribed choroidal hemangiomas by photodynamic therapy or proton therapy: Visual outcomes and tumor control

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Introduction: Circumscribed choroidal hemangiomas (CCH) are rare hamartomas of the fundus. Although CCH are benign, vision impairment is common and can lead to definitive visual loss if untreated. With increasing use of PhotoDynamic Therapy (PDT) since 2000, PBT has gradually been abandoned to be advocated only as salvage treatment. Both treatment modalities have low side-effects. However, PDT can induce irreversible retinal and choroidal atrophy early while radiation-induced toxicities are delayed. We assessed visual and tumor outcomes of CCH.

Methods: Multicentric case-control study of circumscribed choroidal hemangiomas by upfront PDT or PBT.

Results: Of 186 patients, 87 had PDT, 72 PBT (24 observation/3 other treatments). At diagnosis, PDT/PBT characteristics were: age 55/53yo, CCH thickness 2.8/3.7mm p=0.25, diameter 7.2/9.0mm p=0.57, paramacular 54%/71% or parapapillary site 21%/7% p=0.048, with macular edema 28%/40% p=0.137, serous retinal detachment (DSR) 82%/66% p=0.021, exudative retinal detachment 21%/44% p=0.023, visual acuity (monoyer) 0.44/0.39 p=0.08. Follow-up was 93/122months p=0.057. DSR resolved in 72%/51% with PDT/PBT p=0.006 while other associated signs behaved similarly under PDT/PBT. Differential visual acuity and thickness were improved with PBT: -0.20logMAR with PDT/-0.30 with PBT p=0.025 and -1.1mm with PDT/-2.1 with PBT p=0.003.

Conclusion: Despite a massive historical switch toward PDT, the efficacy of upfront PBT appears superior. Propensity score analyses with matching on age, baseline thickness and visual acuity will be available at PTCOG.

PTC58-0577

Clip-less ocular proton therapy: Have we crossed the finishing line?

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Over 30′000 patients have been treated with ocular proton therapy worldwide, with excellent tumor control. The standard procedure (SP) however relies on pre-treatment surgical insertion of surrogate clips, crucial for constructing a geometrical model of the eye/target and for daily target localization. PSI develops a completely non-invasive clip-less workflow, consisting of advanced MRI combined with an optical tracking system (OTS) and dedicated 3D treatment planning system, aiming at improving patient comfort, model accuracy, and overall efficiency.

Clip-less workflow was prospectively benchmarked against the SP for 33 patients. 1.5T-MR-defined target volumes were found to be significantly smaller (volume ratio 0.50 (IQR:0.32)), but overlap with conventional targets. Retinal detachments or small/flat tumors influence target definition and further MRI-sequence improvements and registration with additional imaging techniques may be required, together with rigorous guidelines and/or automated segmentation to decrease inter-observer variability. Whether the SP is too conservative, and/or MRI cannot identify the complete target needs further examination.

The practicability of OTS-based positioning has been shown (success rate $>$96%), however median target-beam alignment accuracy (1.46mm (IQR:1.29)) doesn't yet match the one of SP (0.46mm (IQR:0.39)). While an OTS can be reliably used as a gaze-gating system and for relative verification of the eye position, modifications in OTS design and calibration are being adapted to improve absolute positioning accuracy.

Clip-based workflow remains the gold-standard and benchmarking demonstrates that any modifications need to be handled with maximum care. Nonetheless, substantial improvements have been achieved in development of the clip-less workflow and identified issues seem resolvable from today's standpoint.

Clinics: Lung / Sarcoma / Lymphoma
PTC58-0103

NRG Oncology randomized trials of protons versus photons

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Background: Although proton treatment plans demonstrate lower integral dose than photon plans, few randomized comparative clinical trials have been completed, reflective of the paucity of proton centers (until recently), initial technical limitations constraining patient numbers and clinical sites, some quite rare (i.e. skull base sarcomas), and the inability until IMRT was available for photons to deliver comparable doses to meet equipoise requirements for randomization. With image-guided photon IMRT able to achieve comparable tumor doses, albeit with higher integral dose, many investigators support randomized trials, weighing potential morbidity from higher photon integral dose against the potentially greater proton tumor dose and RBE uncertainty.

Materials and Methods: NRG Oncology is currently conducting four randomized clinical trials of photons versus protons for (1) low grade gliomas, (2) non-small cell lung cancer, (3) esophageal cancer, and (4) hepatocellular tumors. The first is phase II; the others are phase III.

Results: To date (12/31/18)/ target accruals for these studies are: (1) gliomas: 11/120, (2) non-small cell lung cancer: 137/330 (3) esophageal cancer: activation pending/300, and (4) hepatocellular tumors: 15/155 . Factors delaying accrual include patient acceptance of randomization as well as insurance coverage denials for proton treatment for some randomized patients, estimated 30-35% for lung. Strategies to improve accrual include 2:1 randomization protons versus photons (gliomas).

Conclusions: While level one evidence from randomized trials of protons versus photons is considered important to document and quantify the potential advantages of protons versus photons, clinical trials to garner this evidence have been challenging to conduct.

PTC58-0106

Perspectives on the model-based approach to proton therapy clinical trials: A retrospective assessment of a lung cancer trial

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Currently there is a lack of high-level clinical evidence for the benefits of protons over photons for cancer therapy. Although randomized control trials (RCTs) are considered the gold standard of clinical evidence, their appropriateness for investigating the benefits of proton therapy remains controversial. A model-based technique has been proposed as a better approach to detect differences in toxicity between photon and proton treated patients. The aim of this study was to assess whether a model-based approach to patient selection for proton therapy trials is feasible given modeling uncertainties and suggested dosimetric enrollment thresholds. A model-based approach, based on three widely used normal tissue complication probability (NTCP) models, was applied retrospectively to a completed non-small cell lung cancer (NSCLC) RCT (NCT00915005). Patients were assumed to be selected by the model-based approach if their value was above a threshold of 5%. We found that less than 21% (28/136) of patients enrolled in the completed trial would have been enrolled in a model-based trial, prescribing IMRT to all other patients. The number of patients enrolled was also found to be dependent on the type of NTCP model used for evaluating radiation pneumonitis, with the three models enrolling 2%, 15% or 21% of patients (figure 1). Uncertainties in the outcome models to predict NTCP are an inherent drawback of a model-based approach to clinical trials. The impact of these uncertainties on enrollment in model-based trials depends on the predicted difference between the two treatment arms and on the set threshold for patient stratification.

PTC58-0176

Proton beam therapy for Hodgkin lymphoma - reductions in cardiovascular and second cancer risks: Which patients benefit the most?

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Background: Radiotherapy (RT) improves survival in Hodgkin lymphoma (HL), but survivors can be at increased risk of late effects such as cardiovascular disease (CVD) and second cancers. Proton beam therapy (PBT) can reduce radiation exposure of the normal tissues and potentially reduce the risk of late effects. Access to PBT is limited compared to photon RT and referral for PBT must be individualised.

Methods: Normal tissue radiation doses were calculated for 21 HL patients treated with pencil beam scanning PBT in deep inspiration breath hold and compared to advanced photon RT. Disease characteristics that could be used to identify HL patients for whom PBT would give the most substantial dosimetric benefits were identified. Absolute CVD and second cancers risks were predicted using published risk-models. The effect of population background risk was investigated by repeating the calculations using mortality rates from Europe, USA and Japan.

Results: PBT significantly reduced dose to most organs at risk (figure-1) and provided further reductions for patients whose tumor extended below the 7ththoracic level and for patients with axillary disease. PBT reduced mortality risks from CVD and second cancers. The risk reduction varied based on the patients' background risk and disease characteristics (Figure-2).

Conclusions: PBT is not a panacea for all HL patients. Risk predictions may be used to identify which patients may benefit from PBT compared to photon RT. The research here provides the basis for further work towards evidence-based case selection for PBT for HL patients.

PTC58-0580

Pencil beam scanning in the treatment of patients with mediastinal Hodgkin lymphoma: toxicity and early outcome

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Introduction: Pencil beam scanning (PBS) has the potential to decrease doses to the majority of organs at risk. There is a known theoretical benefit for significant subgroup of patients with mediastinal Hodgkin lymphoma (HL). However, clinical experiences with PBS in mediastinal HL are so far limited.

Method: 101 patients (pts) with mediastinal HL were irradiated from 5/2013 to 12/2018. 50 pts (6 males, 34 females) were selected for evaluation of toxicity and outcome with reasonable follow up time (median 40 months). Mean age was 32.4 years, median dose was 30 GyE. RT volumes were: involved field in 9 pts, involved site in 27 pts and residual disease in 14 pts. 35 pts were irradiated to the PET negative volume, 11 pts to the PET positive volume. 33 pts were treated in DIBH (deep breath hold), 17 pts in free breathing.

Results: Toxicity: Acute toxicity (RTOG scale) was mild, in most pts present as moderate dysphagia, radiodermatitis, transient xerostomia. Asymptomatic radiologic changes of lungs occurred on post-treatment CT scans in 6 pts. There was no case of symptomatic pneumonitis or Lhermitt's syndrome.

Outcome**:** 50 pts (100%) are in local control. 48 pts (96%) are in CR, 2 pts progressed out of target volume (1 pt was salvaged by allo-SCT, 1 pt has progressive disease on salvage therapy).

Conclusion: PBS offers safe possibility for mediastinal HL pts with low toxicity profile. PBS with its potential to decrease unintended healthy tissue irradiation should be considered for patients with significant risk of acute and late toxicity.

PTC58-0733

Outcomes of multimodality treatment with induction chemotherapy, maximal resection, and proton based radiation therapy for cardiac and pulmonary vessel sarcomas

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Purpose and Methods: Cardiac and pulmonary vessel sarcomas are extremely rare tumors with poor median survival of 6-12 months. RT is challenging due to OARs and organ motion. We retrospectively reviewed 50 consecutively treated patients between 1975 and 2018 for outcomes, patterns of failure, and toxicity.

Results: Median age was 45 years (8–75). Cardiac subsites were: R atrium 24%, L atrium 22%, R ventricle 4% L ventricle 8%, pulmonary valve or vessels 14%, interventricular septum 2%, SVC/aorta 6%, pericardium 24% with median tumor size 6.0cm (1.5-17.5cm). Patients received surgery+postop RT (46.9%), surgery only (24.5%), RT only (6.1%), or preopRT, resection +/- postop RT (10.2%), chemotherapy (71.%). For RT, 58% received 3D protons (rest 8% IMRT, 6% 3D photons, 6% IOERT) to median dose 64.0 GyE (16-72Gy), 78% with respiratory gating vs 22% without. With median follow-up of 27 months (12–110), overall survival was 64%, 37%, and 28% at 1, 3 and 5 years. Median survival was 28 months. 56.1% developed metastases,17.1% had pleural failure, and 26.8% had local progression. Local control is better with RT to $>=$ 66 Gy(n=23): 80%, 64%, and 52% vs. 25%, 14%, 14% at 1, 3, 5 years for RT $<$ 66 Gy. On MVA, $<$ 5 cm tumor (p=0.036), age $>$ 40 (p=0.028) and non-angiosarcoma (p=0.011) do better. Toxicities included heart failure (15%) with average LVEF 55% (45-76%), arrhythmia (17.1%), valve problems (5.1%), grade 1 radiation pneumonitis (2.5%). None require pacemaker after RT.

Conclusions: RT to a high dose using proton therapy achieves better local control with acceptable toxicities.

PTC58-0200

Carbon ion radiotherapy for sacral chordoma

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Introduction: Chordoma is a rare malignant tumor originating from remnants of embryonic notochord, with predilection for the sacrum. Often en-bloc resection surgery is associated to significant neurological impairment. Recently carbon ion radiotherapy (CIRT) has been used as exclusive therapy reaching similar local control as surgical resection. We present preliminary results concerning response to CIRT for unresectable primary sacral chordoma treated at CNAO (National Center for Oncological Hadrontherapy) in Pavia.

Methods: Between March 2013 and December 2017, 59 patients with sacral chordoma, were treated with CIRT using active scanning beam delivery system at CNAO. The total dose was: 70.4 - 73.6 Gy equivalents (GyE) in 16 fractions. We evaluated tumor response by magnetic resonance (MRI) performed every three months. For each examination, T2w FS axial images were used both to measure lesion maximum diameter and to get a manual segmentation of the tumor. RECIST 1.1 were used to evaluate chordoma response to CIRT. Similarly, the same response criteria were applied to volume modifications for treatment response. The median follow-up period was 24 months (range 12- 60 months).

Results: The preliminary results showed radiological partial response in 38 patients (64%), stable disease in 15 patients (25 %) and progression disease in 6 patients (10%).

Conclusions: Our preliminary data confirm encouraging results of carbon ion treatment for primary sacral chordoma in terms of local control and acceptable toxicity. Longer follow-ups are needed to confirm the effectiveness of CIRT as an alternative to surgery in the absence of late severe side effects.

Biology: Mathematical Modelling Simulation
PTC58-0179

Assessment of clinical RBE variability in proton therapy

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Currently, clinical implementation of a variable relative biological effectiveness (RBE) in proton therapy is controversially discussed. First clinical evidence indicated a variable RBE for brain irradiation, which needs to be substantiated. For assessing clinical RBE variability, we established a normal tissue response model and applied it to follow-up magnetic resonance (MR) images.

Four glioma patients (grade II-III) showing late morphological T1-weighted contrast-enhanced (T1w-CE) MR image changes and suspicious necrosis were considered. All were treated with passive scattering at the University Proton Therapy Dresden (UPTD). Dose and linear energy transfer (LET) were calculated with a TOPAS-based Monte-Carlo (MC) simulation framework dosimetrically validated for UPTD. To establish radiation response, different logistic regression models based on dose and / or LET were trained on T1w-CE MR voxels classified as change (1) or no change (0). Model performance was assessed by the area under the curve (AUC) performing leave-one-out cross validation.

Correlating image changes with dose and LET resulted in a radiation-response model (Fig.1) with high predictive power (AUC=0.87). TD_{50} values (dose at which 50% of patient voxels show toxicity) decreased linearly with LET (Fig.2). Models considering either dose or LET performed only moderately (AUC of 0.68 and 0.64, respectively). LET averaging method (dose-averaged or track-averaged) had no impact on model performance.

Only the model based on dose and LET led to high predictive power for late MR image changes, suggesting a variable radiation response and, hence, non-constant RBE. This study enables and encourages in-depth assessment of clinical RBE variability in proton therapy.

PTC58-0462

Mechanistic modelling of individual cell radiosensitivity and charged particle relative biological effectiveness

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It is well-established that there are significant variations in radiation sensitivity and Relative Biological Effectiveness (RBE) between different tissues. These is driven by both intrinsic effects – individual cell genetics, tissue of origin, and cell cycle phase – and extrinsic micro-environmental effects.

We have developed a mechanistic model of cellular radiation response, incorporating DNA repair and cell death pathways. Significantly, rather than using cell-specific fitting parameters, predictions are based on the cell's phenotype and key genetic mutations. This model simulates the misrepair of DNA double strand breaks (DSBs) in a spatially-sensitive fashion, and by incorporating a Monte Carlo nanodosimetric energy deposition model, cell-specific and radiation-quality specific predictions of RBE can be made.

This model can generate accurate predictions of a range of biological endpoints, including DNA repair kinetics, DSB misrepair, chromosome aberration formation, and cell death. Importantly, as predictions are made without cell-specific fitting parameters, a single model can predict sensitivity in a range of cell lines (R^2=0.74).

The model's RBE dependence was calibrated by fitting it to a dataset of proton RBE measurements, and it was shown that by using these parameters the model can also predict the LET dependence of heavier ions such as carbon, and accurately predict RBE values for a range of cells of different genetic backgrounds and exposure conditions (R^2=0.77).

This approach may provide a foundation for the future development of personalised RBE models.

PTC58-0068

Stochastic microdosimetric kinetic model for hypo-fractionated multi-ion therapy

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The microdosimetric kinetic (MK) model is a biological model used to predict cell-survival fractions from the specific energy absorbed by a microscopic subnuclear structure, domain, for various radiations. The MK model has been used in clinical treatments of carbon-ion radiotherapy at NIRS. While the MK model gives reasonable predictions in biological effectiveness of carbon-ion beams in most clinical cases, discrepancies were found between the calculated and measured cell-survival fractions for high-LET and high-dose irradiations. Recently, we have started a research project of a hypo-fractionated multi-ion therapy (HFMIT) for further developments of heavy-ion therapy. In HFMIT, the heavy ions up to neon ions are considered as the primary beams, i.e., high-LET radiations. In addition, the fractionated dose will be more than 10 Gy (RBE), i.e., high dose. Therefore, we developed a stochastic microdosimentric kinetic (SMK) model that can be used in treatment planning of HFMIT. In SMK mode, the stochastic natures of specific energies both in a domain and a cell nucleus are taken into account. The SMK model could reproduce the measured cell-survival fractions for high-LET and high-dose irradiations. The SMK model was integrated into our research treatment planning system, and tested in the in-vitro experiments of HSGc-C5 and MiaPaca2 cells exposed by scanned helium, carbon, oxygen and neon ion beams. The SMK model and developed computation method offer the accuracy and simplicity required in HFMIT of wide LET and dose ranges.

PTC58-0658

Moving towards an understanding of the influence double strand break end motion has on repair kinetics

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In radiotherapy, the creation of DNA double-strand breaks (DSBs) in a tumor volume is a key objective as unrepaired breaks are believed to be the main driver of cell kill and therefore successful treatment. Working against this lethal pressure are the DNA repair pathways of the cell. The two separated ends of a DSB are predominantly re-joined by either homologous recombination or non-homologous end joining (NHEJ).

The differential efficiency of these pathways between tumor and healthy tissue plays an important role in radiotherapy that is exploited through fractionation. Additionally, the fidelity of repair is important as NHEJ can illegitimately ligate ends from separate, but proximal DSBs. This misrepair can lead to cytotoxic chromosome aberrations or survivable rearrangements of genetic material, possibly contributing to mutagenesis and carcinogenesis in healthy tissues.

Investigation of repair efficiency and fidelity often only consider the recruitment and action of repair proteins. Yet to be fully ligated, the two ends separated from each other by radiation damage must be brought together through motion. No consensus exists on the type of motion that DSB ends undergo other than that it is most likely sub-diffusive. Experimental evidence for both continuous time random walk and fractional Langevin motion has been published, with different underlying mechanisms proposed.

In this work, we use the DaMaRiS modelling framework to show that the exact type of motion plays a critical role in determining overall repair efficiency and fidelity. Given its impact, this question has not yet received proportionate attention in the scientific literature.

PTC58-0357

An analytical approach to model microdosimetric distributions in proton beams for LETd calculation

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Calculation of dose average linear energy transfer (LETd) spatial distributions in proton therapy treatments is becoming interesting recently in order to assess its influence in proton therapy relative biological effectiveness (RBE). Microdosimetry theory provides a framework to address this calculation by using Monte Carlo (MC) simulations. Here we present an analytical approach to model MC-obtained microdosimetric distribution for a fast LETd calculation. Geant4-DNA based MC simulations have been performed to obtain distributions of energy imparted to a spherical site of 1 μm of diameter when a proton traverses it. We model the behavior of the average and standard deviation of these distributions respect to the proton energy. Another function for the track length of the proton within the site depending on the proton energy is proposed. From these three quantities, the dose-mean lineal energy, can be derived. Independently, the dose average energy imparted to the site per collision, $\delta 2$, is also modeled. Finally, LETd can be calculated from yD and $\delta 2$. Figure 1 shows the flowchart to calculate, together with the proposed functions and their fits to the MC data. Results for our model are compared to the MC-obtained values. A remarkable agreement is found proton for energies in which is relatively high, which are presumably the clinically relevant cases. A highly computational-efficient approach is presented to perform calculations of LETd for proton beams from microdosimetry quantities. The accuracy of this model is corroborated, at least, for the highest LET proton energies.

PTC58-0272

Calculating secondary cancer risks after proton and carbon ion beam therapy for liver metastases and prostate cancer patients

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There is an increasing need to understand and estimate radiation-related secondary cancer induction following particle therapy due to the constant improvement of radiotherapy techniques. Compared to proton beams, carbon ion beams take advantage of a lower dose in the entrance channel, a narrower Bragg-peak and a higher RBE. However, they deposit a small dose beyond the distal end of the Bragg-peak due to fragmentation. Differences in dose deposition and RBE can lead to different secondary cancer induction probabilities.

In this study a comparative analysis of the estimated secondary cancer induction probabilities after proton and carbon ion beam therapy was performed for ten patients previously treated for liver metastases and prostate cancer, respectively. The treatment plan optimization was performed with the treatment planning system TRiP98. The risks for secondary cancer induction were calculated assuming a competition between cell survival and the induction of carcinogenic mutations. The risks were estimated for either protons with a constant RBE of 1.1 or protons and carbon ions with a variable RBE based on the Local-Effect Model, which derives the RBE of ions based on the photon response.

The results showed patient-specific secondary cancer induction risks with a tendency towards an increased risk for carbon ion beams compared to proton beams for both cancer types. Despite uncertainties, the study demonstrates the expected impact of both the dose deposition and RBE of the radiation quality as well as patient-specific aspects of the irradiated field on secondary cancer induction risk after radiotherapy.

Biology: Drug and Immunotherapy Combinations
PTC58-0327

The HSP90 inhibitor ganetespib specifically sensitizes cancer cells for clinical SOBP proton beam irradiation in comparison to photon irradiation

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Background: Recent data suggest an elevated dependence on homologous recombination (HRR) to repair DNA double strand breaks (DSB) subsequent to proton irradiation. We investigate the effect of HSP90 inhibition by ganetespib and the role of DNA DSB repair deficiencies for specifically sensitizing cancer cells towards proton irradiation.

Methods and Materials: NSCLC (A549) cells were irradiated with 200kV photon irradiation and a proton pencil beam at a proximal (LET 1,97 keV/μm) and a distal position (LET 4,43 keV/μm) of a 8cm SOBP in a PMMA/water phantom and clonogenic survival fractions were determined. Physical doses are stated and nuclear repair foci assays were used to monitor the DSB repair response.

Results: Inhibition of HSP90 strongly sensitizes A549 cells for proton irradiation within the proximal SOBP. The dose-modifying factor (DMF) at 50%, 10%, and 1% cell survival was 1.18, 1.10, and 1.06 for photons, and 1.17, 1.09 and 1.05 for cells irradiated at the distal position of the SOBP. Interestingly, the DMF was increased to 1.35, 1.22, and 1.16 for cells irradiated at the proximal position of the SOBP.

Conclusions: Administration of ganetespib provides a novel approach to specifically sensitize cancer cells to proton irradiation. Our data suggest that combinatorial approaches induce a differential cellular response when administered with photon respectively proton irradiation. Thus, extensive testing will be required to convert from routine photon protocols to a proton radiotherapy setting.

PTC58-0358

Radiosensitizing pancreatic cancer with PARP inhibitor and gemcitabine: An in vivo and a whole-transcriptome analysis after proton or X-rays therapies

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Purpose/Objective(s): Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with a cumulative 5-year overall survival of less than 5% for all stages. Thirty percent of patients diagnosed with PDAC present with a locally advanced disease could benefit from chemoradiotherapy with gemcitabine, which is effective but toxic. Over the past few years, studies have focused on the development of targeted radiosensitizers such as poly (ADP-ribose) polymerase (PARP) inhibitors. We conducted an *in vivo* study to determine whether PARP inhibition enhances gemcitabine-based chemoradiosensitization of pancreatic cancer xenografts.

Materials and Methods: MIA PaCa-2 cells were injected subcutaneously into the flanks of athymic nude mice. Tumor-bearing mice were treated with gemcitabine and/or olaparib for two consecutive days before irradiation (10 Gy) with either X-rays or protons. Tumor size was measured three times per week. Furthermore, 24 hours after treatment, tumors were excised and fresh frozen tissues were stored. RNA-seq profiling analysis was performed to examine whole-transcriptome alteration.

Results: First, we showed a significant growth inhibition with 10 Gy proton irradiation compared to 10 Gy photon irradiation ($p=0.001$). Moreover, combination of olaparib, gemcitabine and protontherapy significantly sensitizes tumor xenograft compared to either gemcitabine ($p=0.05$) or olaparib ($p=0.05$) alone. Finally, using RNA-seq, process such as cell cycle arrest were found and could be meaningfully related to the regulation of radiation response after proton therapy in pancreatic cancer cells.

Conclusions: The addition of olaparib to proton-based chemoradiotherapy with gemcitabine enhanced local control *in vivo* and could improve disease-free survival. Whole-transcriptome analysis found many cell processes dysregulation after proton therapy.

PTC58-0012

Getting new insights into the radio-sensitization effects of nanoparticles in charged particle therapy using synchrotron-based infrared microspectroscopy

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The use of high-atomic number nanoparticles (NP) as potential tumor selective radio-sensitizers has been proposed as a breakthrough in photon radiotherapy. Recently, the radio-sensitization features of NP have also been explored in charged particle therapy. Indeed, biological experiments combining charged particle beams and NP have shown a clear amplification in the induction of biological damages [1-3]. However, the contribution of physical effects (dose enhancement) remains controversial, and biochemical processes may play a major role in the radio-sensitization effect [4].

Within this context, our objective was to get deeper insights into the biochemical mechanisms underlying the amplification of radiation effects of gold NP in charged particle therapy (proton and carbon beams). For this purpose, we used synchrotron radiation Fourier transform infrared microspectroscopy (SR-FTIRM) as a bio-analytical tool to disentangle the biochemical processes inside glioma cells [5].

Radiotherapy irradiations were carried out at the Heidelberg Ion-Beam Therapy Center (HIT). Regarding SR-FTIRM experiments, the intense infrared light produced at ALBA synchrotron was used, leading to a clear advantage in spectral quality at sub-cellular level. Principal Component Analysis (PCA) showed clear treatment-induced variations in the main cell bio-molecules (Amide I and II protein bands; CH_2 and CH_3 lipid stretching modes; phosphodiester DNA modes), helping to understand the underlying biology of this cutting-edge radiotherapy technique.

Acknowledgements: This project received funding from the EU H2020 programme (Marie Skłodowska-Curie grant agreement *748889)*. References: [1] Usami, Int.J.Radiat.Biol. 83, p.569 (2007). [2] Porcel, Nanotechnology 21, p.085103 (2010).[3] Kim, Phys.Med.Biol. 57, p.8309 (2012).[4] Martínez-Rovira, Med.Phys. 42, p.6703 (2015).[5] Yousef, Analyst 141, p.2238 (2016).

PTC58-0166

The combination therapy using Pitavastatin and carbon ion beam inhibit metastatic potentials on mammary tumor cells

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Breast cancer ranks first among cancer incidence rates in women around the world. Advanced radiation therapy has improved local control at the early stage of the cancer. Once a tumor spreads to another part of the body, i.e. cancer metastasis, poor survival rates become a large problem. Particle beam therapy, such as carbon ion beam therapy, has improved good local control to tumors. However, little is still known about the biological effects of carbon ion related to metastasis. A drug, Pitavastatin, was originally used to improve blood cholesterol levels. Recently it is shown that Statin has the additional effect to shrink breast cancer. Therefore, we hypothesized that Pitavastatin acts as a radiosensitizer for the carbon ion beam and investigated combination effect of the radiation and Statin. As the result of invasion assay, cells irradiated by carbon ion decreased metastatic potential. And a combination of carbon ion and Pitavastatin significantly suppressed invasion capability compared with carbon ion beam alone. Scratch assay showed that Pitavastatin inhibited cell motility at low dose of carbon ion beam. We expect that Pitavastatin might be novel radiosensitizer for breast cancer and metastatic potentials in carbon ion beam therapy.

PTC58-0163

Combination therapy using a dopamine receptor D1 agonist and carbon ion beam inhibit mammary tumor growth and bone metastatic potentials

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Dopaminergic signaling plays a critical role in the nervous system, but little is known about its potential role in breast cancer and bone metabolism. A screening of $\sim$ 1, 000 biologically active compounds revealed that a selective agonist of dopamine receptor D1 (DRD1), A77636, inhibited proliferation of 4T1.2 mammary tumor cells as well as MDA-MB-231 breast cancer cells. Herein, we examined the effect of A77636 on bone quality using a mouse model of bone metastasis from mammary tumor. A77636 inhibited migration of cancer cells in a DRD1-dependent fashion and suppressed development of bone resorbing osteoclasts by downregulating NFATc1 through the elevation of phosphorylation of eIF2α. In the mouse model of bone metastasis, A77636 reduced osteolytic lesions and prevented mechanical weakening of the femur and tibia. Next, we examined the effect of combination therapy using A77636 and carbon ion beam on tumor growth and bone quality. Combination therapy enhanced the tumor cell killing and reduced osteolytic lesions compared to alone DRD1 agonist. Collectively, we expect that dopaminergic signaling might provide a novel therapeutic target for breast cancer and bone metastasis in particle therapy.

Biology: BNCT
PTC58-0063

Clinical veterinary boron neutron capture therapy (BCNT) studies in dogs with head and neck cancer with no other therapeutic option

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Translational Boron Neutron Capture Therapy (BNCT) studies performed by our group and clinical BNCT studies worldwide have shown the therapeutic efficacy of BNCT for head and neck cancer. The BNCT project in Argentina has experience in clinical BNCT studies for melanoma performed at RA-6 Nuclear Reactor. We envision the initiation of a clinical BNCT trial for head and neck cancer in Argentina at RA-6. Within the context of optimizing BNCT for head and neck cancer, putting in place the technical aspects of BNCT for head and neck cancer at RA-6, assessing the feasibility of employing the existing B2 beam for the treatment of deep-seated tumors and/or elucidating the necessary modifications and contributing to the knowledge of BNCT radiobiology, we performed clinical-veterinary BNCT studies in dogs with head and neck cancer with no other therapeutic option. Five dogs with head and neck cancer with no other therapeutic option were treated with two applications of BNCT mediated by boronophenylalanine (BPA) separated by 3-5 weeks. Two – three portals per BNCT application were used to achieve a potentially therapeutic dose over the tumor without exceeding normal tissue tolerance. Irradiation times were adjusted based on blood boron concentration-time profiles. Clinical and TAC results evidenced partial tumor control in all cases with slight-moderate mucositis, excellent life quality and prolongation in the survival time estimated at recruitment. These ongoing studies contribute to the knowledge to initiate, for the first time in America, a clinical BNCT trial for head and neck cancer at the RA-6 clinical facility.

PTC58-0075

BNCT combined with immunotherapy: Evaluation of local, immunologic and cytotoxic effects in an ectopic colon cancer model

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BNCT combines selective tumor uptake of ^{10}B compounds and neutron irradiation. The aim of the present study was to evaluate the local therapeutic efficacy, abscopal effect and cytotoxicity of BNCT combined with Bacillus Calmette-Guerin (BCG) as immunotherapy in the BDIX rat ectopic colon cancer model. BDIX rats were inoculated with syngeneic colon cancer cells in the right hind flank. Four weeks post-inoculation the tumor bearing rats were treated, i.e. BNCT-group: BNCT mediated by borono-phenyl-alanine (BPA) at RA-3; BNCT+BCG-group: BNCT+three intratumoral applications of BCG; BCG-group**:** BCG only**;** Beam only-group (BO-group): irradiated without BPA; BO+BCG-group**;** Sham-group: same manipulation, no treatment. Two weeks post-BNCT, colon cancer cells were inoculated in the contralateral left hind flank to assess abscopal effect. Tumor volume was measured in both legs weekly. Seven weeks post-BNCT the animals were euthanized; samples were taken for histology and proximal lymph nodes were evaluated. A cytotoxicity test was carried out with splenocytes and colon tumor cells. BNCT, BCG and BNCT+BCG groups exhibited significantly greater local tumor response and abscopal effect vs Sham-group ($p<0.05$). The percentage of animals with metastatic spread in proximal lymph nodes was significantly lower in the BNCT-group (11%) and the BNCT+BCG-group (10%) vs Sham-group (48%), ($p<0.05$). The BCG and BNCT+BCG groups exhibited the highest percentage (43%) of animals that recover normal toxicity levels vs Sham-group (28%). The present study demonstrated that BNCT and BNCT combined with immunotherapy induce robust therapeutic and abscopal effects. A trend towards potential synergy between BNCT and immunotherapy was observed and warrants further study.

PTC58-0085

Therapeutic effect of BNCT mediated by maleimide-functionalized closo-dodecaborate albumin conjugates (MID:BSA) in the hamster cheek pouch oral cancer model

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Introduction: Oral cancer has poor overall 5-year survival rate and surgery causes large tissue defects. BNCT (Boron Neutron Capture Therapy) combines selective tumor uptake of 10-B compounds and neutron irradiation. Nowadays, the development of new, more tumor-selective, non-toxic boron delivery agents is necessary for the progress of BNCT. Nakamura et al. developed maleimide-functionalized *closo*-dodecaborate (MID) for conjugation to bovine serum albumin (BSA), and showed high and selective accumulation in tumor with a significant effect of BNCT in colon tumor-bearing mice. Our group demonstrated therapeutically useful tumor boron concentration values and tumor/normal tissue ratios in the hamster cheek pouch oral cancer model. Herein, we assessed the therapeutic and radiotoxic effect of BNCT mediated by MID:BSA in the hamster cheek pouch classical oral cancer model.

Materials and Methods: Cancerized hamster cheek pouches were exposed to BNCT-MID:BSA (15mg^{10}B/kg) at (A) 2.6 Gy and (B) 6 Gy absorbed dose to precancerous tissue. We evaluated the therapeutic effect of BNCT on tumors and the associated radiotoxicity.

Results: BNCT-MID:BSA was nontoxic and did not induce severe mucositis. The % of tumor overall response 21 days post-BNCT was dose-dependent, i.e. Group A -60%- and Group B -76%-. The % of tumors that reduced their volume by more than 50% was 48% (Group A) and 71% (Group B).

Conclusion: BNCT-MID:BSA was therapeutically useful to treat tumors in the hamster cheek pouch oral cancer model with no associated toxicity. Future studies will include dose-escalation studies to enhance tumor control.

PTC58-0567

Brain tumor stem like cells may take up boronophenylalanine, a clinically used drug for BNCT

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Introduction: Chemo- and radio-resistance of brain tumor stem cells could be the origins of recurrent malignant glioma. We have used boron neutron capture therapy (BNCT) to treat patients with either recurrent or newly diagnosed malignant glioma, resulting in a significant increase in median survival of patients. BNCT is a form of tumor-selective particle radiation therapy consisting of two components. First, a boron-10 (^{30}B)-containing drug is administered, followed by irradiation with epithermal neutrons. The resulting ^{30}B(n,α)^{7}Li capture reaction produces alpha particles whose short path length (5–9 μm) results in the selective killing of tumor cells. P-boronophenylalanine (BPA) is a chemical compound used in clinical trials in BNCT. Here, we investigate whether brain tumor stem like cells take up BPA or not using mass cytometry (Cytof).

Methods: We used brain tumor stem like cells (SLC) and the cells differentiated (DC) by fetal bovine serum from them. After exposure to BPA for 24 hours at the concentration of 25ppm in 5% CO2 incubator, we immune-stained them using twenty stem cell markers, anti-Ki-67, anti-BPA and anti-CD98 (heterodimer that forms the large neutral amino acid transporter to take up BPA) antibody and analyzed with Cytof.

Results: Two to three times larger number of SLC were BPA or CD98 (+) than DC. In BPA or CD98 (+) cells in SLC, the number of stem cell marker (Oct3, Nestin, Sox2, and PDGFRa) (+) cells were two to six times larger than negative cells

Conclusion: Stemness may influence the uptake of BPA.

PTC58-0596

Phase II clinical study of boron neutron capture therapy combined with X-ray radiotherapy/temozolomide in patients with newly diagnosed glioblastoma

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Boron neutron capture therapy (BNCT) is biologically tumor selective particle irradiation using nuclear capture and reactions inside the one-cell level.

In our previous study, we reported the efficacy of combination therapy with external beam X-ray irradiation and BNCT. Based on these results, we planned this Phase II prospective study named "Boron Neutron Capture Therapy, Radiation Therapy, and Temozolomide in Treating Patients with Newly Diagnosed Glioblastoma" (OSAKA-TRIBRAIN0902, NCT00974987).

After the administration of boron-10 containing drugs BPA and BSH, neutron irradiation was performed. The limiting factor for the irradiation time was settled for the normal brain dose as 13 Gy-Eq. The primary endpoint is overall survival and these patients were followed up for 2-years after the last patient treatment.

Analysis of the primary endpoint was a hazard rate test for significance on overall survival from BNCT treatment. As a result, it was shown that "the hazard ratio of BNCT treatment (0.0328) is smaller than the standard treatment (0.0542)" ($p = 0.0120$). That is, it is indicated that BNCT treatment has a higher therapeutic effect (has a prolongation effect) than standard treatment. As a result of the conversion into the survival rate, the survival rate (at 24 months) was 27.3%, the BNCT treatment was 45.5% (29.9 - 59.9), the lower limit 29.9 of the 95% confidence interval was 27.3% And the survival rate of BNCT treatment was higher than the survival rate of the standard treatment. The survival rate at 24 months of BNCT treatment estimated using the Kaplan - Meier method was 30.2% (95%CI: 14.4, 47.7).

PTC58-0474

Biological dose models for predicting normal tissue complication probability in head and neck cancer BNCT

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Boron neutron capture therapy (BNCT) is based on accumulation of a boron carrier in cancer and subsequent neutron irradiation. The first accelerator-based neutron sources suitable for hospital use have been developed.

Radiation dose in BNCT consists of four components: 1) the high-LET dose from $^{10}B(n,a)^{7}Li$ reaction, 2) nitrogen capture dose, 3) recoil proton dose and 4) photon dose. Traditionally, the biological dose is obtained as a sum of dose components after multiplying each with a constant RBE or a (boron) compound biological effectiveness (CBE) factor. An alternative biological dose calculation method, the photon iso-effective dose formalism, takes into account the dose rate and the cumulative dose per fraction using the first-order repair of sublethal lesions in the modified linear-quadratic model, and considers synergistic interactions.

We applied the photon iso-effective dose formalism to calculate the normal tissue complication probability (NTCP) for the mucosal membrane for 30 patients with recurrent HN carcinoma, who were treated with BNCT. The NTCP predicted by the two dose calculation methods were compared with the observed mucositis at 4 to 5 weeks after BNCT.

Grade 3 mucositis was observed in 8 (27%) out of the 30 patients after the first BNCT. The maximum physical dose to the mucosal membranes was 3–6 Gy. Corresponding RBE doses were 8-14 Gy(W) predicting $\geq$grade 3 mucositis for 0.03 patients. The iso-effective doses were 12-18 Gy(IsoE) predicting $\geq$grade 3 mucositis for 7 (23%) patients.

The photon iso-effective dose model predicted mucosal membrane toxicity after BNCT more reliably than the traditional RBE model.

Biology: Enhanced Biology in Treatment Planning

PTC58-0258

Kill-painting of hypoxic tumors with multiple ion beams

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The concept of the prescribed dose in radiotherapy was extended in the past years towards more realistic quantities, approaching a biologically effective dose. Recent developments, such as LET painting or kill painting, try to push the concept of biologically oriented treatment planning, to sub-volumes of different sensitivities.

We present a novel method for biological optimization using multiple ion species, aiming at improving the treatment planning for heterogeneously oxygenated tumors. In this context, the kill painting approach, optimizing the overall biological effect on hypoxic targets, was expanded. Now it is capable of handling ion beams with different physical and radiobiological properties, such as the decreased fragmentation of the light ions or the higher RBE and LET values of the heavier ions, simultaneously. We report the results of the treatment planning studies, as well as the first *in vitro* experimental verification of this approach performed at MIT, Marburg.

The treatment planning studies were carried out using the updated version of the GSI research treatment planning system TRiP98, augmented to handle voxelized target oxygenation data. Studies with idealized geometries, as well as the *in silico* studies with patient plans have shown, that the uniform biological effect can be achieved by forwarding the heavier ion modalities to hypoxic target areas while covering the normoxic areas preferably with lighter ions, resulting in the most optimal LET distribution in the target. In certain cases, this might lead to the improvement of the peak-to-entrance effective dose ratio and the reduction of the dose received by critical structures.

PTC58-0519

3D-printing and validation of a solid phantom for experimental proton beam irradiation

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Accurate, reproducible and easy-to-use experimental setups across teams and institutions for radiobiological assays are necessary in order to advance the understanding of biological responses to particle radiation. Development of silicone molding by 3D-printing would allow for fast production and flexible shapes for fast adaptation to variable experimental conditions. In this work, various 3D-printed and silicone rubber materials were characterized in terms of proton stopping power, absorption and biological inertness. The water-equivalent ratio (WER) of the 3D-printed materials was around 1.17 while the WER of the silicone rubbers was close to water. The 3D-printed and silicone materials show increased scattering compared to high-density polyethylene. Silicone rubbers provide biological inertness while the 3D-printed materials were toxic when in contact with cells. Thus, the ProtoCellRack, a flexible solid silicone phantom design for cell irradiations was produced using a 3D-printed mold and validated. A specifically designed treatment plan assures dose homogeneity across the target area in the solid phantom (5.13 – 5.37 Gy). An apoptosis cell assay was used to biologically validate the dose conformity over the designed spread-out Bragg peak. The flexibility and ease of fabrication of those materials should accelerate interdisciplinary projects across centers for reproducible experimental conditions in radiobiology and will advance our understanding of biological responses to protons.

PTC58-0246

Conversion of dose constraints for organ at risks between different biophysical models for prostate carcinoma (PCA) patients receiving carbon ion radiotherapy

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Purpose: To investigate methods for converting carbon ion relative biological effectiveness (RBE)-weighted doses out of the clinical target volumes (CTVs) from different biophysical models for PCA patients.

Material and Methods: The micro-dosimetry kinetic model (MKM) provided by Raystation was matched with the published data; local effect model (LEM) in Raystation was compared to the LEM in Syngo. Cube-phantom studies were used to evaluate the difference. Ten previously treated PCA patients were involved for making carbon ion treatment plans using MKM (NIRS plans) with different prescriptions to CTVs; then LEM calculated the RBE-weighted doses based on the physical doses from NIRS plans (SPHIC plans). The conversion factors (LEM doses divided by MKM doses) from CTVs were compared to the published data; the RBE-weighted isodose conversion out of the CTVs were obtained by relating the isodose curves from NIRS plans to the isodose curves from SPHIC plans having the same volume guided by the theoretical analysis. The Rectum dose constraints from NIRS were converted based on the curves and compared to treated dose volume histograms (DVHs) from 10 patients (treated DVHs).

Results: The maximum deviation of cube-phantom studies was 2.86%. Our conversion factors for CTVs were consistent with the published results. A curve converting the RBE-weighted doses from MKM to LEM out of the CTV was established. The treated DVHs of rectums were below the converted dose constraints, which matched the patients' clinical outcomes.

Conclusions: For PCA patients, carbon ion RBE-weighted doses in MKM could be converted to doses in LEM.

Biology: Translational and Biomarkers
PTC58-0287

Image-guided stereotactic proton irradiation of mouse brain sub-volumes validated by cell-based DNA damage analysis

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In proton therapy, an intense debate is ongoing to what extent toxicity originates from clinical margins, range uncertainties, and varying relative biological effectiveness (RBE). To contribute decisive preclinical arguments, we established stereotactic proton mouse brain irradiation and cell-based DNA damage analysis.

A setup to shape a proton beam with a 7 mm range in water and 3 mm in diameter was built and dosimetrically characterized. Computed tomography and orthogonal X-ray radiography were used to delineate the target (right hippocampus) and to position the mice. Proton radiography enabled alignment of target and beam axis. For two mouse strains (C57BL/6; C3H), brains were irradiated with 0, 4 Gy or 8 Gy and excised after 30 min or 3 h. Brains were sectioned; DNA double-strand break repair and cell nuclei were visualized by staining (gH2AX and DAPI). Imaged section analysis (Fiji-Software) provided maps with spatially resolved ratios of DNA-damaged to total number of cells.

Twenty mice underwent the treatment workflow including imaging, target delineation, positioning (head fixation), and irradiation (Fig.1). The spatially resolved DNA damage patterns matched the measured dose distributions. For C3H mice, the proton beam hit the right hippocampus and stopped in the brain. Damage pattern were spatially more extended and diffuse for 8 Gy and 3 h after irradiation, respectively (Fig.2). C57BL/6 mice showed larger spatial variation in beam-to-target alignment.

We established biologically validated stereotactic proton irradiation of mouse brains for translational normal tissue and RBE studies. Cell-based assessment and geometric accuracy enable biologically and spatially resolved radiation response analysis.

PTC58-0514

Examining the differential cellular response of pancreatic cancer cell lines to 12C vs. photon irradiation

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Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy that is expected by 2020 to become the second most common cause of cancer-related deaths globally. The 5-year overall survival rate for patients with PDAC is <10%, which is due to the majority of pancreatic cancer patients presenting with advanced disease and the inherent resistance of PDAC to conventional chemotherapy and radiotherapy. Clinical trials from Japan have suggested that carbon ion radiotherapy (CIRT) used concurrently with gemcitabine is effective against unresectable locally advanced PDAC. Recently, UTSW has initiated a multi-institute, randomized Phase III clinical trial, called CIPHER, that aims to compare CIRT to IMRT (intensity-modulated radiation therapy) for treating locally advanced, non-resectable PDAC. In conjunction with CIPHER, we have started pre-clinical studies to identify ways to enhance CIRT radioresponsiveness based upon underlying genetic features. In particular, we have focused on examining the role of an aberrant DNA damage response (DDR) in PDAC treatment responsiveness. This is supported by exome sequencing data of >150 surgically excised PDACs that showed that >35% of PDAC tumors have an alteration in a DDR gene and that these alterations correlate with a poor outcome. In this study, we utilized eight PDAC cell lines, whose survival fraction of 2 Gy (g-rays) ranged from average to radioresistant, to determine if CIRT can overcome photon radioresistance and to identify DDR-related biomarker(s) that predict responsiveness to CIRT. Furthermore, we will present data examining targeted DNA repair inhibitors to potentiate CIRT-mediated cell killing of g-rays resistant cell lines.

PTC58-0345

Carbon ion radiotherapy for prostate cancer was analyzed by differential proteomics

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The individualization of radiotherapy treatment would be beneficial for PCa patients. However, there are no predictive biomarkers of carbon ion radiotherapy (CIRT) effects in routine clinical use. This study describes the plasma proteomics, which have been used for finding biomarkers for patient stratification according to prognostic risk. In this study, quantitative mass proteomics was used to detect the plasma of 19 patients with localized PCa before and after CIRT. Differentially expressed proteins were screened for functional annotation and bioinformatics analysis, and their correlation with efficacy was evaluated. A total of 1,680 proteins were identified and quantitatively. Patients were divided into two groups with good response and weak response according to the expression level of PSA for differential proteomics analysis, and pathway enrichment analysis was performed for the final 122 proteins. The results showed that AMPK, Ras, MAPK, Rap1 and PI3K Akt signaling pathways and the PPAR signaling pathway involved in T cell interaction were closely related to CIRT, and there were significant changes in a large number of immune-related proteins. ROC analysis further showed that multiple plasma proteins had the potential of CIRT prognostic biomarkers, especially IGFBP5 and FAP (AUC > 0.8). This study is the first to use proteomics to evaluate CIRT for prostate cancer. It was found that plasma protein expression profile was significantly affected by CIRT, and might be a potential prognostic biomarker of CIRT. This work was supported by the National Key R&D Program of China (2017YFC0107600), the National Natural Science Foundation of China (81773225).

PTC58-0599

The role of proton therapy to preserve ovarian function and reserve in mice

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Purpose: X-ray radiotherapy (XRT) of tumors close to ovaries causes reproductive and other sequelae from ovarian primordial follicle (PF) depletion. Given its finite range, proton therapy (PRT) may preserve ovarian function when ovaries are positioned beyond the SOBP. This study compared 1) PF survival in ex-vivo mouse ovaries following XRT vs. PRT, and 2) anti-Müllerian hormone (AMH) levels (biomarker of ovarian function) following in-vivo mouse pelvic XRT vs. PRT.

Methods: Forty-four (44) ex-vivo ovaries from day-5 mice and 66 day-21 live mice were divided into controls, XRT, PRT to ovaries in the SOBP plateau, and PRT to ovaries beyond the SOBP. For ex-vivo experiments 0.2Gy was prescribed. Surviving PFs were counted. For in-vivo experiments, 1.8Gy was prescribed. Ion chambers and post-treatment CT scans verified PRT dose. AMH was measured at baseline and 3-weeks post-treatment. ANOVA with Tukey's Multiple Comparison test compared PF counts and AMH.

Results: In ex-vivo ovaries, PF counts following 0.2Gy-PRT to ovaries beyond the SOBP were equivalent to controls ($p=0.8$), while counts following 0.2Gy-XRT ($p<0.001$) and 0.2Gy-PRT to ovaries in the SOBP ($p<0.001$) were significantly reduced. In live mice, relative to controls 3-week post-treatment AMH was significantly lower following 1.8Gy-XRT ($b=-2.4$ng/ml, $p<0.001$) and 1.8Gy-PRT to ovaries in the SOBP plateau ($b=-2.4$ng/ml, $p=<0.001$), but was equivalent following 1.8Gy-PRT to ovaries beyond the SOBP ($p=0.4$).

Conclusions: When positioning ovaries beyond the SOBP during PRT, ovarian function and PF reserve are preserved. Validation of these findings is being tested in a clinical trial of PRT for tumors close to ovaries.

PTC58-0244

Investigation of cardiac troponin T in NSCLC patients who received IMRT or PSPT – secondary analysis of a prospective randomized trial

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Purpose/Objectives: We investigated potential associations between serum high-sensitive troponin T (hsTnT) levels and survival, cardiotoxicity in NSCLC patients receiving definitive chemoradiation therapy (CRT).

Materials and Methods: Cardiotoxicity and serum hsTnT were evaluated before, during and after CRT in a prospective clinical trial of NSCLC. Cardiotoxicity were graded according to CTCAE 4.0. Serum samples were assayed with hsTnT (Roche Diagnostics).

Results: In total, 190 patients were included in this analysis. Radiation doses in the range of 60-74Gy were delivered with IMRT or PSPT. The median of mean heart dose (MHD) was 12 (range 0-41) Gy. The median follow-up time was 28 (range 2-102) months. Pre-treatment hsTnT was higher in males, elders, and patients with pre-existing heart diseases or poor performances. Throughout CRT, hsTnT was gradually increasing (coefficient=0.35 weekly, P=0.01). The maximum percent change of hsTnT during CRT from baseline was correlated with MHD (P=0.006). hsTnT levels increased by 62% more in patients with left lung tumors than those with right lung tumor (P=0.028). Cardiotoxicity occurred in 58 (31%) patients with incidence rates of 17% and 14% for grade>=2 and grade>=3 respectively. The median follow-up to cardiac events is 9 (range 0.3-32.6) months. The risks of cardiotoxicity and mortality were increased if elevated serum hsTnT (>10ng/L) were found at any timepoint or hsTnT increased >=5ng/L during CRT.

Conclusions: Elevation of hsTnT during CRT related to MHD. hsTnT was strongly predictive of cardiotoxicity and mortality at any timepoint. Early monitoring of hsTnT could identify patients who are more sensitive to cardiac damage from radiation.

Biology: Biological Differences between Carbon / Proton and Photons Carbons / Proton and Photon

PTC58-0517

Mitochondrial targeting may sensitize lymphoma cells to proton therapy

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Mitochondria are the only extra nuclear sites containing dsDNA, and contain multiple cell survival/apoptosis regulatory components. Published reports have demonstrated that mitochondrial damages can occur following ionizing radiation but no comparison of photon vs particle radiation effects on mitochondrial damages or implication of such damages on proton RBE has been made so far. Our recent transcriptomic analyses of lymphoma cells treated with X-ray, proton or carbon ions revealed unique gene expression patterns suggesting mitochondria involvement specifically in particle therapy response.

To further explore the effects of targeting the mitochondrial repair mechanisms by proton radiation, we compared proton vs X-ray irradiation effects on mitochondria. Following a single physical dose of 5 Gy of X-ray or proton irradiation, we observed a depolarization of the mitochondrial network in live cells using high resolution confocal imaging, and detected an increased apoptosis rate after proton irradiation comparing to X-ray. Interestingly, the observed increased apoptosis correlated with increased mitochondrial DNA damage and increased mitochondrial mass, with prolonged oxidative stress and elevated protein oxidation after proton irradiation. L67 drug inhibition of LigIII activity, the sole DNA ligase mediating mitochondrial DNA repair, sensitized lymphoma cells to proton irradiation with an increased apoptosis rate.

These results suggest that increased RBE of proton radiation are in part a consequence of pronounced damage to mitochondria and may be applicable to multiple tumor types. Combinatorial targeting of mitochondria damage repair pathways may thus sensitize tumor cells to proton therapy, with a reduced risk of genomic mutations and clonal expansions of tumor cells.

PTC58-0129

Preliminary study on the radiosensitivity of carbon ion in human breast cancer

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Aims: To investigate the various effects of high linear energy transfer (LET) carbon ions ($^{12}C^{6+}$) and low LET X-ray radiation on human breast cancer MDA-MB-231 and MCF-7 cells and to explore the underlying mechanisms of radiation sensitivity.

Main Methods: Cell proliferation, cell cycle distribution, cell apoptosis, and expression level of γ-H2AX as a marker of double-strand break formation, cell cycle–related protein CyclinB1, and apoptosis-related protein Bax and Bcl-2, as well as the activation levels of the Akt/mTOR/p70s6k pathway, were detected after irradiation with carbon ions or X-ray at doses of 0, 2, 4, and 8 Gy.

Key Findings: Our results showed that cell proliferation, G2/M phase arrest, DNA lesions, and cells apoptosis/necrosis induction elicited by carbon ion irradiation were more efficient when compared with X-ray radiation at the same dose. Simultaneously, carbon ion radiation induced a remarkable increase in Bax and prominent decreases in cyclin B1 and Bcl-2 in a dose-dependent manner as compared with X-ray. Furthermore, the Akt/mTOR/p70s6k pathway was significantly inhibited by carbon ion radiation in both breast cancer cells.

Significance: These results indicate that carbon ion radiation has prominent superiority over X-ray in killing breast cancer MDA-MB-231and MCF-7 cells, and which might result from the inhibition of the Akt/mTOR/p70s6k pathway.

PTC58-0216

Deciphering cellular response to raster-scanning proton, helium, carbon and oxygen ion beams via integrative transcriptomics, proteomics and phospho-proteomics

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Molecular mechanisms governing particle irradiation induced intracellular signaling remain elusive. Within this work we performed a radiobiological characterisation of the effects of particle beams focusing on the irradiation-induced –omics signatures of therapeutic (proton and carbon), and experimental (helium and oxygen) ion beams at Heidelberg Ion-Beam Therapy Center (HIT).

To assess the biological efficacy of the beams and define relative biological effectiveness (RBE), series of different radiobiological readouts (e.g., clonogenic assay, DNA damage response signalling) have been performed, using human lung cancer cells. As a reference irradiation quality, photon irradiation was performed using a linear accelerator (LINAC, 6 MV). For irradiation with proton, helium-, carbon- and oxygen ion beams, cells were positioned in the middle of a 1 cm wide SOBP centered at about 3.5 cm water-equivalent depth. Plans have been optimised applying a research treatment planning system available at HIT. Transcriptome (Illumina microarray) and (phospho)-proteome (SILAC and high-resolution mass spectrometry) analyses were performed. Early (phospho)-proteome signature (2h post-irradiation) was investigated using doses inducing same biological effect (SF_{30} doses for photons:6Gy, protons:3.5Gy and carbon ions:2Gy). For comparing photon, proton, helium, carbon and oxygen beams, biologically optimised SOBP was used to minimize the effects of possible range uncertainties on biological readouts (transcriptome and (phospho)-proteome at 6h and 72h post-irradiation). Coherent transcriptome and proteome signatures were observed. Phospho-proteome indicated alterations in apoptosis and metabolic processes induced by photons and particle beams. Our data mark a starting point for further functional characterisation of mechanisms underlying radiation quality specific cellular response to particle therapy.

PTC58-0524

Enhancing 12C radiotherapy for head and neck cancer via biomarkers of radioresponse, targeted agents, and conditional vulnerabilities

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Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide. Despite recent advances, roughly 30% of patients will experience recurrence for which median survival is less than one year. Factors contributing to treatment failure include inherent resistance to X-rays and chemotherapy, hypoxia, EMT, and immune suppression. The unique properties of ^{12}C radiotherapy including enhanced cell killing, a decreased oxygen enhancement ratio, generation of complex DNA damage, and ability to overcome immune suppression and EMT following exposure make its application well suited to the treatment of HNSCC. We examined the ^{12}C radioresponse of six HNSCC cell lines, whose surviving fraction at 3.5 Gy ranged from average to resistant when compared to a larger panel of 49 cell lines. To determine whether ^{12}C irradiation can overcome X-ray radioresistance and whether there may be tumor biomarkers predictive of ^{12}C radioresponse. Cells were irradiated with ^{12}C using a SOBP with an average LET of 75 keV/μm (CNAO: Pavia, Italy). RBE values at 10% survival ranged from 2.13 to 4.2 with an average RBE of 3.06. DNA damage foci resolution suggested that unrepaired, complex double strand breaks contribute to an enhanced RBE relative to photons. A comparative analysis of gene expression post-^{12}C exposure vs g-Rays revealed differential regulation of DNA double strand break repair, differentiation, cell cycle progression, and cell death modulation. Based on the above analysis, we present the framework of a strategy to utilize biological markers to predict which HNSCC patients would benefit the most from ^{12}C radiotherapy.

PTC58-0570

IGFBP5 regulates radiobiological effects of prostate cancer with carbon ion radiotherapy through the PI3K-AKT pathway

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Background: With the advantage of physics and radiobiological effects, carbon ion radiotherapy is a precision therapy for prostate cancer. However, the mechanism and radiobiology of carbon ion radiotherapy are unclear. It is urgent to elucidate these radiation responses.

Methods and Material: To explore carbon ion radiotherapy radiobiological response, proteomics was induced to analyze the differential expression of proteins before and after radiotherapy. Plasma sample was collected before and after radiotherapy in 19 patients with localized prostate cancer. Mass spectrometry was used to detect these plasma sample. Cluster and pathway analysis is used to describe the differential expression. To study differential proteins' function in radiotherapy, prostate cancer cell lines PC3 and DU145 received X-ray radiotherapy, carbon ion radiotherapy and proton radiotherapy.

Results: Cluster analysis demonstrated 122 differential expressed proteins. AUC curve discriminates IGFBP5 with prognostic potential. And high expression of IGFBP5 was associated with immediate efficacy (PSA$<$0.2ng/ml). Pathway analysis indicated that these proteins mainly associated with PI3K-Akt pathway. IGFBP5 inhibited proliferation and induced cell cycle in prostate cancer. Overexpressed IGFBP5 enhanced radiosensitivity in PC3 and DU145 cells. Whether IGFBP5 affect prostate cancer cells' radiosensitivity after carbon ions or proton therapy is understudy.

Conclusion: In present, we found high expression of IGFBP5 referred to immediate efficacy and overexpressed IGFBP5 enhanced radiosensitivity after X-ray radiotherapy. It may regulate these responses via PI3K-Akt pathway. This work was supported by the National Key R&D Program of China (2017YFC0107600), the National Natural Science Foundation of China (81773225).

PTC58-0016

Novel insights into the cellular response to complex DNA damage induced by high-LET protons

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Proton beam therapy displays variations in energy and linear energy transfer (LET) via the Bragg peak leading to different biological effects. In particular increases in complex DNA damage (CDD), where several lesions are induced in close proximity within DNA, contributes significantly to the therapeutic effect of protons due to the difficult nature of its repair. Despite this, very little is known about the mechanism of recognition/processing of CDD in cells within chromatin.

Utilising the 60 MeV cyclotron at the Clatterbridge Cancer Center, we have comparatively analysed the response of HeLa and head and neck squamous cell carcinoma cells to low-LET (58 MeV, 1 keV/μm) protons generated at the Bragg peak, versus high-LET (11 MeV, 12 keV/μm) protons generated at the distal end. Data has also been correlated with high-LET α-particle and low-LET x-ray irradiation. We have demonstrated that high-LET protons induce significant decreases in cell survival post-irradiation versus low-LET protons due to elevated levels of CDD. We have identified that CDD is signalled by histone H2B ubiquitylation on lysine 120 mediated by the E3 ubiquitin ligases RNF20/40 and MSL2, which plays vital roles in co-ordinating CDD repair and in controlling cell survival. Furthermore utilising an siRNA screen of enzymes controlling ubiquitylation (~94 deubiquitylating enzymes), we have identified that USP6 is required for maintaining cell survival specifically in response to high-LET protons which is mediated through stabilisation of poly(ADP-ribose) polymerase-1 (PARP-1). We also demonstrate synergy of the PARP inhibitor olaparib in combination with high-LET protons in significantly increasing cancer cell killing.

Biology: Biology and Clinical Interface

PTC58-0719

Early experience with the addition of locoregional deep hyperthermia to pencil beam scanning protons in pelvic and abdominal tumors

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Introduction: Hyperthermia is a well-known radiosensitizer when delivered concurrently with radiation. Our group recently commissioned a Locoregional Deep Hyperthermia (DHT) unit in a Pencil-Beam Scanning Proton Therapy (PBT) facility. This combination has the potential to improve outcomes for advanced or recurrent malignancies.

Methods: Retrospective single institution IRB-approved review of all patients treated with concurrent DHT and PBT. All patients were required to have locally advanced or recurrent abdominal or pelvic tumors with the ability to measure temperature within the tumor or a proximal intracavitary surrogate. We collected patient characteristics and DHT parameters, including maximum temperature (Tmax) and maximum thermal dose (TDmax), to evaluate acute toxicity in an initial patient cohort.

Results: Nine patients received DHT/PBT with a median age of 70 years (19–75). Histologies included rectal cancer (n=5), sarcoma (n=2), bladder cancer (n=1) and prostate cancer (n=1). Seven patients (78%) were treated with re-irradiation. Median PBT dose was 40.8 Gy(RBE) (31.2-57.0) and seven (78%) received twice daily PBT. Median number and therapeutic time of DHT were 5 (1–8) and 33 min (0-65), respectively. The target Tmax achieved on average 40.9°C (38.3-43.7°C). Acute toxicities included grade 1-2 pain (n=7), diarrhea (n=4) and dermatitis (n=3). With a median follow up of 2 months (range, 1-3 months) there have been no reported local failures or deaths to date. Updated outcomes and toxicities will be presented.

Conclusions: Initial combination of DHT with PBT is well tolerated and toxicities during treatment have been mild. Continued follow up is required to assess late toxicities and treatment related outcomes.

PTC58-0454

Inflammatory response dynamics in early-stage lung cancer patients after treatment with proton versus photon radiation

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We compared time-dependent changes in normal lung parenchyma of early-stage non-small cell lung carcinoma (NSCLC) patients after stereotactic body radiation therapy using protons (SBPT) or photons (SBRT).

NSCLC patients treated at our institution with SBPT were retrospectively identified and matched to SBRT patients based on all relevant clinical characteristics. Follow-up computer tomography (CT) scans were deformably registered with the treatment plan to analyze lung density changes as function of dose, quantified by the average increase in Hounsfield Unit (HU) as a function of dose (HU/Gy). In addition, the CTs were evaluated by a thoracic radiologist using an established grading system.

23 SBPT/SBRT pairs were matched, including 5 patients treated with both modalities (internally matched cohort). Normal lung response following SBPT significantly increased early (median 3 months) post-treatment and stayed constant thereafter. Density increase in SBRT patients were also significant at the early timepoint but, contrary to SBPT, kept increasing up to later time points (median 9 months, $p=0.003$). These differential response dynamics were most pronounced in sensitive (response $>$6HU/Gy) patients and in the internally matched cohort. However, there was no difference in the maximum observed response in the entire cohort over all time points, median 3.1[IQR, 1.1-5.9]HU/Gy (SBPT) versus 2.9[1.7-5.2]HU/Gy (SBRT). Differences between modalities tended to be more pronounced in low-dose regions ($<$15 Gy,$p=0.05$).

Our data support the hypothesis that a subset of lung cancer patients exist in whom proton radiation causes a more pronounced early inflammatory response in the normal lung. The clinical significance and potential therapeutic implications warrant further study.

PTC58-0663

Hyperthermia increases sensitization of proton beam therapy in chordoma cell lines

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Introduction: Chordomas are rare malignant tumors, commonly found in the clival and sacrococcygeal regions. The current standard of care is limited to en-bloc resection followed by adjuvant Radiotherapy (RT). However, chordoma is highly radioresistant. Hyperthermia (HT at 39-43°C) acts as a potent radiosensitizer and increases tumor blood perfusion. Proton beam therapy (PBT) mitigates RT induced toxicities due to its characteristic spread of Bragg-peak (SOBP). We investigated whether PBT response can be further be enhanced in combination with HT as a radiosensitizer and also tumor cell killing at the end of the SOBP compared to the middle of the SOBP of PBT with HT.

Method: Human Chordoma cell lines, U-CH2 and Mug-chor1 were treated with HT followed by PBRT at both middle and distal SOBP with the dose of 4, 8, 12 and 16Gy for U-CH2 and 1, 2, 4, and 8Gy for Mug-chor1. Colony forming assay was performed for the dose response survival.

Results: HT significantly ($p<0.05$) decreased colony survival in combination with PBT at both middle and the distal SOBP for both cell lines. In U-CH2, HT with PBT significantly killed ($p<0.05$) cells at doses 4 and 8Gy and for Mug-Chor1 ($p<0.05$) at 1, 2 and 4Gy at both middle and distal SOBP. We also found that Mug-chor1 is more heat-sensitive and radiosensitive while U-CH2 is heat-resistant and radioresistant.

Conclusions: Our results provide the first-time in vitro evidence about the effects of HT as a novel additive treatment to increase PBT effectiveness in Chordoma cell lines.

PTC58-0685

NTCP models of late rectal morbidity after proton therapy in 1,036 prostate cancer patients

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Background: Photons and protons have fundamentally different properties (reduced dose bath with proton therapy (PT) and a higher relative biological effectiveness (RBE)). Photon-based normal tissue complication probability (NTCP) models might therefore not be applicable to PT. The aim of this study was therefore to derive parameters of the Lyman-Kutcher-Burman (LKB) NTCP model with prospectively recorded late morbidity data from PT, focusing on rectal morbidity and prostate cancer.

Materials and Methods: Dose volume histogram data for the rectum and rectal wall from 1036 prostate cancer patients (no anti-coagulant treatment) treated with PT and with prescribed target doses of 78-82Gy (RBE=1.1) in 2Gy fractions. LKB model parameters were derived for two alternative late grade 2 rectal bleeding endpoints (CTCAE v3.0): Grade 2A (GR2A) was classified as medical (e.g. prescribed suppositories) and Grade 2B (GR2B) was classified as procedural (included minor cautery and topical formalin application).

Results: Late GR2A+2B rectal bleeding was observed in 155/1036 patients (15%) and GR2B in 45/1036 patients (4%). The volume parameter n was low (0.04-0.14) both for GR2A+2B and GR2B, and lowest for GR2B for the rectum. For uniform irradiation of one-third of the rectum (V=1/3) an NTCP of 5% was found at 59Gy for GR2A+2B and at 75Gy for GR2B (Fig. 1). There was a close to 1:1 relation between calculated NTCPs and observed morbidity (Fig. 2).

Conclusion: PT specific NTCP model parameters for prospectively recorded late rectal morbidity in more than 1000 patients were derived. The volume parameter was generally small indicating a weak volume effect, most pronounced for the GR2B endpoint.

PTC58-0490

New horizons in fast neutron therapy

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The University of Washington (UW) Clinical Neutron Therapy System (CNTS) has been in continuous clinical operation since October of 1984 and treated over 3,200 patients. The CNTS was the first hospital-based cyclotron with the ability to deliver 3D conformal neutron therapy using a multi-leaf collimator (MLC), wedges and gantry capable of 360° rotation about a patient (isocenter). When compared to the primitive field-shaping techniques used in most clinical trials prior to 1984, the 3D conformal treatments possible using the CNTS reduce Grade 3+ morbidity for the treatment of localized treatment of carcinoma of the prostate to levels comparable to MV x-ray treatments. Over the past few years, we have put in place most of the technological pieces necessary to delivery robust, accurate, and practical intensity modulated neutron therapy (IMNT) treatments. We expect to introduce IMNT into routine clinical practice in 2019, which will create exciting new opportunities to improve the therapeutic ratio of fast neutron therapy (Figure 1). Fast neutron therapy, a high linear energy transfer (LET) radiation with a relative biological effectiveness (RBE) comparable to carbon ions, has shown promise for the treatment of tumors resistant to MV x-rays (Figure 2, left panel), and we are also seeing evidence in the clinic and from translational research efforts that fast neutrons are effective at stimulating anti-tumor activity when combined with immunotherapy (Figure 2, right panel). Monte Carlo simulations suggest that IMNT in combination with the delivery of tumor-specific boron agents may further boost the effectiveness of neutron therapy.

PTC58-0479

Analysis of recurrences in proton therapy of non-small cell lung cancer

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Purpose: To evaluate the effects of approximations in analytical dose calculations algorithms used in current clinical Treatment Planning Systems (TPS) on treatment outcomes in lung patients treated with passively scattered proton therapy.

Methods: We analyzed 23 patients with loco-regional recurrences from the proton arm of a randomized trial comparing overall survival after photon versus proton chemoradiotherapy. Dose distributions computed with the clinical TPS were compared with dose distributions computed with more accurate Monte Carlo methods using dosimetric indices based on a dose-volume histogram analysis. Recurrence regions were contoured on post treatment PET-CT images and deformably registered to the planning CT. The differences in mean dose, EUD10 (equivalent uniform dose with a = -10), and V100 (volume covered with 100% of the prescription dose) for the internal gross tumor volume (iGTV), internal target volume, planning target volume (PTV), and the recurrence volume (RV) were used in the analysis.

Results: The mean doses predicted by TPS were within 5% of corresponding MC doses for all volumes considered in the analysis. However, we found that TPS consistently overestimated the target coverage with cohort average values of 2.1%, 9%, 20.6%, and 7.5% for iGTV, ITV, PTV, and RV respectively.

Conclusion: Our results indicate that analytical dose calculation algorithms used in current treatment planning systems underestimate the scattering in the beam line and the heterogeneous thorax geometry, which results in underdosing of target volumes with differences increasing from iGTV to PTV. The difference in coverage of the recurrence volume indicates a possible clinical effect of these differences.

Scientific: RTT
PTC58-0641

Pediatric patient ramp-up at the Groningen Proton Therapy Center: The Dutch experience

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Introduction: In January 2018 proton therapy was clinically introduced in The Netherlands at the University Medical Center (UMC) Groningen. That same year, another key event was the centralization of all Dutch pediatric oncology care at the Princess Maxima Center (PMC) in Utrecht. Here we report our experience in the first year after the introduction of proton therapy.

Organization of Care: The pediatric radiation oncologists from the UMC Groningen and UMC Utrecht together form the radiation team of the PMC. This team makes decisions on the preferred treatment modality. A plan comparison is used only when deemed necessary. All proton-based treatments are delivered in Groningen.

The Groningen Proton Therapy Center (GPTC) is an integral part of the UMC Groningen Comprehensive Cancer Center. A multidisciplinary team at the UMC Groningen monitors all patients. Anesthesia and paramedical support, in-patient care and family housing is available on site. Chemotherapy is delivered by the department of pediatrics.

Results: Pediatric care has received priority during the preparation phase, enabling an immediate clinical start with pediatric patients including cranio-spinal treatments and treatments under anesthesia. The first patient started treatment in January 2018. By the end of the first year 51 patients started treatment. Anesthesia was used in 21 patients. We were able to deliver treatment to all Dutch patients making international referrals unnecessary.

Conclusion: In the first year of operation we were able to provide timely proton therapy treatment to all referred pediatric patients.

PTC58-0637

Impact of practice CT date on anesthesia utilization for pediatric patients

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Background: For pediatric patients undergoing radiation therapy the treatment planning scan requires the child to stay motionless, as does daily treatment with proton therapy. For children aged 8 or less, the Radiation Therapists would attempt to work with the child to get through the CT simulation without anesthesia. If this was found not to work, the patient would undergo CT with anesthesia and proceed with daily anesthesia for treatment.

Interventions: A structured, practice CT was established as of January 16th, 2017.

Evaluation: The day of practice CT simulation, time is scheduled for Child Life to meet with the patient.They use age appropriate explanations as well as visual aids to guide the patient through what will happen, then work with the child throughout CT simulation to help them tolerate the procedure. Two attempts at scans without anesthesia are performed. If patient is unable to tolerate the scan after the second attempt, the patient will complete the CT simulation, as well as daily proton therapy treatment, under anesthesia.

Discussion: Based on pre-screening by intake, 23 out of 46 children aged 4-9 were determined to be viable candidates for receiving an official structured practice day. Of these 23 children, 22 have successfully completed their CT simulation, and subsequent treatment, without anesthesia. This translates into a 97% success rate.

Innovation: This process has reduced the treatment burden on the child and family by eliminating the need for daily anesthesia, thus reducing the total treatment time and treatment cost.

PTC58-0612

The regression patterns of pediatric optic pathway glioma after proton beam therapy

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Background: Pediatric optic pathway glioma (POPG) is frequently treated with radiotherapy (RT). We evaluated the radiographic response and clinical outcomes after proton therapy (PBT).

Material and Methods: A total of 11 POPG patients treated with salvage or definitive PBT were included. The median age of RT was 7 (range, 3-16). Eight patients (72.73%) had previous chemotherapy, 2 patients (18.18%) underwent partial resection and/or chemotherapy, and one patient received PBT alone. All patients took regular MRI at 3-4 months and then yearly up to 5 years. The tumor control, radiographic patterns, time to radiographic response, and late side effects were examined.

Results: The median follow-up was 53.5 months (range, 27.7–131.7). The median radiation dose was 54 GyE (range, 54-59.4). Three patients developed local recurrence with a median latency of 45 months (range, 5.6-85.4). The radiographic response of total volume was variable. In most patients, cystic volume developed after treatment and increased in median time of 42 months (8/11 patients, time range, 24-60). Three patients had cyst fenestration and intervention due to symptoms from cyst enlargement. However, the solid portion decreased in 8 patients with the time of 50% volume reduction in median 28.84 months (range, 12.77-82.28). Preserved visual acuity was observed in 8 patients, the one patient had the complete visual loss, and the others had decreased visual acuity.

Conclusion: The radiographic regression patterns of POPG after RT involved significant cystic change. Response evaluation after treatment needs to be measured for both solid and cystic volume of tumors.

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PTC58-0388

Three-year experience in daily image-guided proton therapy with robotic cone beam CT: Development and optimization of clinical workflow

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Purpose: Our half-gantry, pencil-beam scanning proton system incorporates a novel ceiling-mounted, gantry-independent, robotic cone-beam CT (CBCT) for image guidance. CBCT imaging can be performed at 3 locations including 2 positions offset 27cm and 100cm from the beam isocenter. Workflow optimization and experience are reported.

Methods: The imaging location was selected according to the patient's disease site and the position on the treatment couch. Patient position was corrected daily with CBCT using 3D-3D image registration applying 6 DOF couch shifts. The patient was subsequently moved by robotic couch to the treatment isocenter. Couch positions for patient treatments were captured during the verification-sim, at the treatment isocenter as reference for site setup.

Results: Over 500 pediatric patients have been treated over three years. Timely transfer of CBCT dataset and DICOM spatial registration objects to OIS were implemented, which facilitates physician offline review of CBCT image of the day superimposed on planning CT. For multi-isocenter treatment such as CSI, the total room time including daily 3-isocenter CBCT guidance has decreased from 2 hrs initially to slightly over 1hr. Couch coordinates after imaging were saved in irradiation control software for subsequent retrieval. This allows easy and safe return to the first treatment site after completing image guidance at all isocenters.

Conclusions: We successfully established a clinical workflow for a unique gantry-independent robotic CBCT system and performed image guidance at and away from the radiation isocenter. Off-isocenter imaging locations present unique challenges for clinical workflow, which was overcome through joint collaborative efforts of users and vendors.

PTC58-0503

Lessons learned from setting up the first high energy proton center in England

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After any project it is good practice to review and look at successes and improvements needed. The best part about learning a lesson from a project is the potential to improve on the next project. These successes can identify best practices to apply to future projects and be shared with the community. Recording the reasons behind project improvements or issues is also important to documenting lessons learned. Identifying a project issue isn't enough—understanding where the issue originated and the impact it had gives more context to the issue and helps set up recommendations for improvements moving forward. The increase demand for proton therapy has motivated many health care systems, both private and public, to provide proton therapy treatment and centers continue to be developed at pace. As of January 2019, PTCOG [1 report] there are 47 particle centers under construction and 21 in the planning stages. The Christie NHS Trust will share with the community lessons learnt from developing a 3-gantry proton center. 1. https://www.ptcog.ch/index.php/facilities-in-planning-stage; https://www.ptcog.ch/index.php/facilities-under-construction accessed on line January 2019.

General: New Investigator Session

PTC58-0320

Lung stereotactic body radiotherapy (SBRT) using spot-scanning proton arc (SPArc) therapy: A feasibility study

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Purpose: To exploit the feasibility and potential clinical benefits of using spot-scanning proton arc (SPArc) therapy for lung stereotactic body radiotherapy (SBRT).

Methods: Eight lung SBRT patients treated via volumetric arc therapy (VMAT) were used. Both Intensity Modulated Proton Therapy (IMPT) plan based on single field uniform dose optimization technique and SPArc plans were generated using robust optimization with parameters of ±3.5% range and 5mm setup uncertainties. 4800cGy relative biological effectiveness [RBE] was prescribed to target in 4 fractions. To assess patient breathing-induced target motion on treatment dose delivery, a 4D dose was calculated by mimicking the organ motion with the scanning spot beam delivering. To exploit the potential dosimetric benefit of using SPArc over the current SBRT practice VMAT, organ at risk (OARs) were compared. Treatment delivery time was calculated simulating from machine mechanical parameter.

Result: SPArc significantly mitigate the breathing induced interplay effect compared to IMPT. The D99 via single-fraction 4D dynamic dose was 4824cGy[RBE](SPArc) vs 4694cGy[RBE](IMPT)($p = 0.03$). SPArc is capable of providing similar target coverage but better OARs sparing (Table 1) compared to VMAT or IMPT. Specially, SPArc significantly reduced the Dmean of ipsilateral lung by 168cGy[RBE] ($p < 0.001$) (VMAT) and 93cGy[RBE]($p < 0.001$) (IMPT) respectively (Figure 1 and Table 1). SPArc delivers much more spots with a significantly lower MU weighting compared to IMPT (Figure 1(d)).

Conclusion: SPArc has the potential to further reduce ipsilateral lung mean dose over VMAT. It could mitigate the interplay effect and open an option of hypofraction treatment for mobile lung tumor using proton therapy.

PTC58-0673

The radiosensitization effect of internalized gold nanoparticles in proton therapy

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One of the biggest challenges in conventional X-ray based radiotherapy is the delivery of a curative dose to the tumor while limiting the adverse effect on surrounding healthy tissue. Therefore, proton beams allow improvement of radiotherapy outcomes due to their characteristic inverted depth-dose profile. In addition, enhancing the sensitivity of the tumor to proton radiation by using gold nanoparticles (AuNPs) could overcome limitations of low linear energy transfer (LET) protons to treat radioresistant tumors. While most of studies focused on AuNPs and X-rays up to now, a handful of theoretical simulation studies investigated the radiosensitization effect of AuNPs in combination with proton beams. To the best of our knowledge, there are currently no radiobiology studies on AuNPs and proton beams with an energy relevant to clinical practice (>60 MeV).

This *in vitro* study investigated the potential radiosensitization effect of 50 nm AuNPs (10μl/ml) on CHO-K1 cells in combination with a clinical 200 MeV proton beam. AuNP internalization by the cells was confirmed by inductively coupled mass spectrometry and transmission electron microscopy. AuNPs and protons decreased the clonogenic cell survival by 31.1±8.7% compared to proton irradiation alone. Additionally, cells were irradiated at different positions along the proton depth-dose curve to investigate the LET-dependence of AuNP-radiosensitization. An increase in cytogenetic damage was observed at all depths for the combined treatment compared to protons alone. However, this was only statistically significant at the entrance plateau and the proximal position of the spread-out Bragg peak ($p < 0.001$) and in the distal fall-off region ($p < 0.01$).

PTC58-0630

A new prompt gamma-ray detection system for 3D range verification in proton beam therapy

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Over the course of a fractionated treatment anatomical changes can severely impact the delivered dose distribution from that planned; evaluation of these changes on a fraction-by-fraction basis is essential. We report the first results of a new method to determine proton beam range in three dimensions, for pencil-beam scanning systems. The range is determined through the reconstruction of the origin of prompt gamma (PG) rays emitted from nuclear de-excitations following proton bombardment.

The prototype system is comprised of 16 symmetrically-spaced $LaBr_3$(Ce) detectors, in a spherical design. The position reconstruction capability of the detector system was initially investigated by means of Monte Carlo Geant4 simulations. To determine the PG-rays emission positions in 3D, the information recorded by each detector is fed into an in-house developed reconstruction algorithm.

Simulation results show that for a spectrometer with realistic energy and time resolution the algorithm is capable of reconstructing the position of an isotropic ^{60}Co source to within 1 mm in 3D space. Figure 1 shows the reconstructed position of: (a) a source located in (0, 0, 0), (b) a source shifted by 20 mm along all directions. In addition, the system performance with a 180 MeV beam impinging a water phantom was investigated in silico. As shown in Figure 2 an excellent agreement was observed between the algorithm-reconstructed PG-rays emission positions (dot-dashed curve), the PG-rays emission positions scored by the phantom (dashed curve) and the dose distribution (solid curve). The next stage is to test the system with a beam experimentally.

PTC58-0339

Proton patient log file analysis for machine performance evaluation

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Introduction: Treatment log files for spot scanning proton therapy provide a record of delivery accuracy, but they also contain diagnostic information for machine performance. A collection of patient log files can identify machine performance trends over time. This may facilitate identification of machine issues before they cause downtime or degrade treatment quality.

Methods: At our facility, all patient treatment logs are stored in a database in DICOM format. These log files contain information including the gantry, spot position, monitor units (MUs), and gantry angle. Software was developed to extract the spot position, MUs, and gantry angle from all log files. The mean spot position deviation and MU deviation were calculated for each delivered field. A total of 15 months of treatment on 4 gantries was analyzed, including 30,100 total fields. The data was analyzed to identify trends, which were then correlated with QA measurements and maintenance records.

Results: A gantry angle dependence of +/-0.5mm in the spot position was identified for two gantries (Figure 1). A sub-millimeter drift in the spot position deviation was also identified. MU deviations were identified after the implementation of a new multi-energy beam extraction method. The maximum per spot deviation from planned MUs in the positive and negative directions increased by 0.0005 MUs (Figure 2).

Conclusions: We have used patient treatment log files to identify trends in machine performance in a spot scanning proton therapy facility. Future work will include developing log file analysis metrics to preemptively diagnose performance issues and continuously monitor system performance.

PTC58-0252

Development of an integrated prompt-gamma imaging and positron-emission-tomography (PG-PET) system for in-vivo dose verification

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To fully utilize the potential advantage of proton therapy, accurate dose prediction in real-time is necessary. As representative methods for in-vivo dose verification, prompt-gamma-imaging (PGI) has high accuracy in range prediction, while detection efficiency is low, and positron-emission-tomography (PET) is able to easily estimate three-dimensional (3-D) dose distribution, while the accuracy is low. Therefore, we proposed a PG-PET system that combines the advantages of the two methods and optimized a detector module using Monte Carlo method.

The optimal detector module was determined by Geant4.10.00 simulation using 150MeV proton beam and water phantom. The detector module was composed of a 2-D scintillator array covering 64x64 mm^2 area, two silicon photomultiplier arrays for dual-ended readout, and a parallel-hole collimator. To reduce the background level, optimal energy and time thresholds were determined and a depth-of-interaction (DOI) technique was proposed.

As a result, 200mm thick of collimator with 8mm pitch of array were determined. For the sensitivity of the system, 7mm width of collimator hole and the 30mm thick of GAGG scintillator array were selected. When 3-7MeV energy thresholds, 2ns time window, and DOI technique were applied, the background was reduced by 14.88%, 17.38%, and 57.36%, respectively compared to the standard condition. Finally, we obtained 3-D PG and PET images with 16 detector modules (figure1) and offer the possibility of integrating PGI and PET systems, which is undergoing for the empirical test with the therapeutic proton beam.

PTC58-0548

Modelling immunofluorescent staining of DSB damage for proton therapy: Are we seeing the whole picture?

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Immunofluorescent tagging of DNA double-strand break (DSB) markers, such as the phosphorylated form of histone H2AX (γ-H2AX) and p53-binding protein 1 (53BP1), are powerful tools in understanding biological consequences following irradiation. However, whilst the technique is widespread, there are many uncertainties related to the ability to resolve and reliably deduce the number of DSBs when using such markers. This study evaluates the impact of the linear energy transfer (LET) of the incident radiation and the ability of automated foci counting software to accurately score the number of DSBs.

Simulations of the DSB distributions following exposures of 2 Gy of protons at varying LET were generated. For each DSB distribution, a corresponding DNA repair simulation was run and the un-repaired DSBs were recorded at several time points. The microscopy image was then generated by our computational microscope which emulated a Zeiss Airyscan confocal microscope. The microscope produces a mock immunofluorescent image at a central Z-slice of a single cell. The generated image is then analysed by foci counting software, and compared to the actual number of DSBs present.

A comparison of the number of incorrectly counted foci was performed for varying LET for different time points (Figures 1–2). The most incorrect counts for each time point occurred for very high LET (21.7 and 25.9 keV/μm). The results show that, on average, as the LET increases so does the number of incorrectly counted foci. This computational evaluation will be expanded to explore other microscopes, other foci counting software and off-axis microscopy methodologies.

General: New Horizons Session

PTC58-0191

Proton beams in magnetic fields: comparison between GATE/Geant4 calculations and dosimetric measurements

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Introduction: Proper prediction and compensation of beam lateral deflections are essential for magnetic resonance guidance in particle therapy. This work aims to develop a Monte Carlo (MC) model describing a clinical proton beam in the presence of static magnetic fields up to 1T and benchmark it against experimental dosimetric data.

Material and Methods: Measurements were carried out using proton beams (62.4 – 252.7 MeV) with a dipole magnet (B=0-1T) positioned at the room isocenter. A PMMA phantom (200×120×300 mm^3) was placed in the center of the magnet, assuring homogeneous magnetic field irradiations (Fig. 1). To account for fringe fields, the GATE8.0/Geant4 MC toolkit was extended to include vector fields maps supplied by the manufacturer. Gate/Geant4 simulations were validated against measurements using a plane parallel ionization chamber and Gafchromic EBT3 films in two beam modalities: single energy fields and spread out Bragg peaks.

Results: Simulated longitudinal and lateral dose profiles agreed very well with measurements (Fig. 2). Range and dose–weighted average differences were below 0.5 mm and 2.1% respectively for all irradiations. The central beam position and width differed less than 1 and 0.5 mm respectively to the measurements.

Conclusion: The MC model was successfully benchmarked to experimental data and will be used to generate reliable basic input datasets for a treatment planning system, accounting and compensating for beam deflections due to magnetic fields.

PTC58-0347

Planning and delivery of FLASH in a clinical ProBeam: A preclinical study

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Background: Recent studies have shown apparent reduced tissue toxicity associated with ultra-high dose rate irradiation of 40-100 Gy/sec, with equivalent or improved tumor control. Published studies to date have used customized laboratory platforms. This work presents the feasibility of delivering FLASH dose rates on a clinical Probeam with pencil beam scanning

Materials and Methods: In this toxicity study, gender matched mice were treated with protons in transmission at 0, 15, 17.5 and 20 Gy at both FLASH (50 Gy/sec) and conventional (0.5 Gy/sec) proton dose rates, using a clinical Probeam operating at 245 MeV. Dose rates were confirmed with a Pyramid faraday cup, and doses were measured using gafchromic film and a parallel plate ion chamber. The pencil beam planning was performed on a Moby digital mouse phantom in Eclipse, with a lung V100 of 80% and respective max doses to the spleen, gut and brain of 5 Gy, 11 Gy and 15 Gy (figure below).

Results: Differential inflammatory responses were observed in the FLASH vs. Conventionally treated groups, with the female mice responding better to the FLASH irradiation than the male mice. This difference was most apparent in the overall survival as illustrated by the Kaplan-Meier curves shown below.

Conclusion: This study has shown the feasibility of delivering FLASH dose rates with protons on a clinical Probeam in the plateau region of the Bragg peak. The FLASH irradiation seems to exhibit lower toxicity than conventional proton irradiation, and this difference seems to be more enhanced in female mice than males.

PTC58-0522

Integrated MRI and proton therapy: Modeling and experiments of pencil beam scanning in an MRI field

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Purpose: MRI-guidance is currently being pursued for its promise to improve the targeting precision of particle therapy. At OncoRay in Dresden (Germany), a 0.22 T clinical MRI scanner has been positioned at the end of a horizontal pencil beam scanning (PBS) proton beamline. The aim of this work is to model and experimentally assess the perturbations of scanned pencil beams caused by the static magnetic fields of the MRI scanner.

Methods: Proton pencil beams (70-220MeV) were transported through the magnetic field of the scanner. EBT3 film was used to detect the beam paths downstream at a beamstop (Fig1d). A Monte Carlo model (Geant4) was integrated with magnetic modeling (COMSOL) to simulate the experimental setup for comparison (Fig1a-c).

Results: Fig1b shows examples of the beam deflection through the MRI for scanned 70 MeV proton beams. The simulations consistently slightly under-predicted the measured deflection at the end of their paths (6-21 mm, see Table1), possibly due to an underestimation of the fringe field strength in the magnetic field modeling.

Conclusion: Modeling the perturbation of proton pencil beams by MRI scanners is inherently a complex process, dependent entirely on having accurate models (or maps) of the magnetic field of the MRI scanner and particle beam parameters. Experimental verification of modeling predictions is paramount to having confidence in future applications such as dose planning for clinical treatments inside the MRI scanner. In this study, for the first time, we have been able to investigate this process, giving confidence in advancing this prototype modality.

PTC58-0563

Towards FLASH proton therapy: Exploring dose rate distributions for different treatment plan and PBS machine characteristics

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Purpose: To investigate spatially varying instantaneous dose rates for different IMPT planning strategies and delivery scenarios, and compare these to FLASH irradiations (>30 Gy/s).

Methods: For a head and neck case, dose rates were calculated for clinically applied (33,855 spots) and spot-reduced (1,006 spots) IMPT plans. For both, different delivery scenarios have been simulated: constant beam intensity (PSI-Gantry 2), variable beam intensity per energy-layer or per spot (assuming currently achieved Varian ProBeam intensities on PSI-Gantry 3), and spot-wise varying, unrestricted intensities such that spot times are always kept ≤3ms. For each voxel in the plan, the 'dose-weighted dose rate' (referred to as 'weighted dose rate') was calculated, defined as the sum of the spot-wise instantaneous dose rates weighted by their dose contribution to the voxel. All dose rates were calculated assuming a 1.8 Gy_{RBE} fraction dose.

Results: For the original clinical plan (PSI-Gantry 2), average weighted dose rates of ≤1.7 Gy_{RBE}/s were calculated (Figure 1). However, for the spot-reduced plan, as higher beam intensities can be utilized, average weighted dose rates in healthy tissue ranged from 0.7 to 14.3 Gy_{RBE}/s, depending on the delivery scenario. Comparable dose rates were observed for the PTV. Highest values were found at beam entrance and at the distal end of each field, the latter being potentially beneficial for adjacent/overlapping organs-at-risk (Figure 2).

Conclusion: FLASH dose rates are not achieved for conventional planning on PSI-Gantry 2. As such, energy-layer or spot specific beam intensities, higher fraction doses and/or spot-reduced plans are required to approach FLASH compatible rates.

PTC58-0321

Theoretical study at the nanometer scale of photon, high-energy electron, and proton minibeam radiation therapy

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Minibeam Radiation Therapy (MBRT) is an innovative radiotherapy technique leading to remarkable normal tissue sparing. The irradiation is performed by using an array of parallel thin (400 to 700 μm) beams. In this work, Monte Carlo simulations were used to assess the micro- and nano-dosimetric characteristics of this distinct dose delivery approach using different beam types (photons, electrons, protons), to help understanding the biological effects involved. Irradiations with photon (effective energy of 69 keV), electron (300 MeV) and proton (100 MeV) minibeams (MBRT, eMBRT, pMBRT) were simulated using the Geant4-DNA extended code. Cells containing spherical nuclei with or without a detailed description of DNA geometry were placed at different depths in peak and valley regions (Figure 1).

Figure 1

Both mean energy deposition and DNA damage in the valley cell nuclei were found very low compared to the peak region for the three approaches in the first five centimeters, while only the charged beams can reach similar effects in peaks and valleys after seven centimeters to favor tumor control. At nanometric scale, eMBRT and pMBRT produce direct clustered Single Strand Breaks (SSBcplx) and Double Strand Breaks (DSB) while MBRT seems to lead to a majority of isolated SSB. In peak regions, protons produce more DNA damage per primary particle and the complexity of breaks increases with depth, unlike electrons that lead to constant proportions of complex damage in depth (Figure 2).

Figure 2

These results could help the understanding of the biological data being acquired.

PTC58-0420

Can interlaced proton grid therapy plans pass all the clinical goals set by IMPT standards?

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Purpose: To evaluate the potential clinical validity of interlaced proton grid therapy plans based on realistic clinical goals used for IMPT plans.

Material and Methods: CT data from previously treated patients were reused. The dataset consisted of five patients presenting tumor growths in different locations (oesophagus, right lung, liver, prostate and anus). For each patient, one IMPT plan and four interlaced proton grid plans, with different interlacing geometries, were created with the treatment planning system RayStation v4.6, resulting in a total of 25 plans. The same clinical goals for the OARs (QUANTEC) and PTV were used for both the IMPT and proton grid plans in the optimization. The clinical validity of the interlaced proton grid plans on a dosimetric level was evaluated, and their differences with corresponding IMPT plans was assessed.

Results: Of the 20 grid plans computed, 18 passed all clinical goals set for the PTV and OARs. The remaining two failing plans were found in the liver case, where the close proximity of the duodenum prevented the use of some grid angles (failing of $D_{0.1cc}<24$ Gy goal). For the PTV, the homogeneity index was $4.0\pm0.9\%$ for the IMPT plans and $8.3\pm2.1\%$ for the proton grid plans. The OARs dose distributions were in some instances significantly different between the two techniques, but remained well below the goals set.

Conclusion: Based on dosimetric considerations only, it is possible to produce interlaced proton grid therapy plans that are clinically acceptable with regards to clinical goals used for current IMPT treatments.

PTC58-0390

Design-based economics for proton beam therapy centers

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Despite the changes in proton system sizes and trend towards one room systems outside large academic institutions, the commercial decision to add PBT remains a very significant financial and operational commitment in an uncertain future. Successful proton projects are based on evidence from comprehensive initial evaluations such as clinical requirements including clinical outcomes, operational services and total project viability and economics.

Proton centers mainly fail to get off the ground because their design-based economics are overshadowed by the technology and the equipment. We will review causes for commercial failure and how to incorporate design-based economics to ensure a project is delivered successfully on schedule and on budget.

Our experience globally and at the Christie taught us that there are several decisive preliminary stages of a proton project intrinsic to success:

1. A client-specific feasibility study and market analysis based on local demographics
2. A client-specific, market analysis-based business model and proforma calculated on national healthcare and/or private insurer reimbursements
3. The selection of the proton equipment based on clinical requirements for their patient's needs
4. A right-sized design that respects the economics of the institution, justifies the expenditure, and meets the projected future patient demand

In determining the economics of a proton project, the overall project costs and capital expenditure often contribute significantly to short term problems and often long-term failure.

Experience and history have taught us that proton centers are too often over-designed with massive project costs and debt service that fundamentally prohibit the center from being fully utilized and profitable.

PTC58-0720

Concurrent pencil beam scanning proton therapy and hyperthermia: A new frontier in particle therapy

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Purpose: Hyperthermia (HT) has been regularly used as an excellent radiosensitizer with conventional radiotherapy (RT). There is a paucity of safety/efficacy data for the concurrent use of proton therapy (PT) and HT due to the lack of institutions with capabilities for both modalities. We report, herein, the largest, and growing, clinical experience with concurrent Pencil Beam Scanning Proton Therapy (PBS-PT) and HT to date.

Methods: At our institution, PBS-PT has been utilized in over 1,400 patients, of which 30 courses/sites (25 curative, 5 palliative) have been delivered with concurrent superficial-HT in 27 patients. Histologies include sarcoma (n=11), breast (n=9), vulvar (n=1), skin (n=1), mesothelioma (n=1), ovarian (n=1), head/neck (n=1), anal (n=1), and ureteral (n=1) cancers. PBS-PT doses ranged from 36 to 70.2 Gy(RBE) (median 57 Gy[RBE]) including altered/hypo-fractionation. The BSD-500 platform was utilized for all superficial-HT administrations (median 8, range 4-28 HT sessions per course).

Results: With a median follow-up of 7.4 months (range 1-31 months), concurrent superficial-HT and PBS-PT has been well tolerated. There were no acute/subacute grade 4-5 toxicities. Grade 3 toxicity arose in only 5 patients: acute desquamation (n=3), chronic lymphedema (n=2). Grade 1-2 toxicities included radiation dermatitis, pain, hyperpigmentation, and GI disturbance. Twenty-two patients (81.4%) remain alive, while 20 (74.1%) are locally controlled and 18 (66.7%) remain free of disease.

Conclusion: Concurrent PBS-PT and superficial-HT is well tolerated. While long-term follow-up and prospective data are needed, superficial-HT has represented a safe adjunct to particle therapy in the largest institutional experience to date with this combination.

PTC58-0578

An investigation into the feasibility of oxygen depletion as the mechanism behind FLASH

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FLASH radiotherapy has become a hot topic in radiotherapy. It has been suggested that the use of ultra-high dose rates may have normal-tissue-sparing advantages over conventional irradiation, while maintaining the same level of damage to the tumor. Recent reports of an increased differential response between normal tissue and tumor cells in mice have attracted widespread attention to the advantages of FLASH. Despite these results, there exists a distinct lack of understanding of the underlying mechanisms behind this effect.

Oxygen depletion induced by ultra-high dose rate provides a promising explanation. Many early reports have discussed this as a possible mechanism, but this has not been fully investigated in recent studies. The extensive wealth of knowledge of the radiobiological effects of hypoxia make oxygen depletion a worthwhile hypothesis to investigate further.

This work is aimed at determining whether oxygen depletion can feasibly explain the tissue-sparing effect of FLASH. Cellular automata techniques have been employed to model the complex processes of oxygen diffusion and reaction, and how these are affected by ultra-high dose rate irradiation. Preliminary results suggest that the effect of dose rate on oxygen concentration in cells is significant, with ultra-high dose rates causing temporary depletion. This work allows us to test hypotheses about the potential mechanisms behind the FLASH effect. A mechanistic understanding is essential for developing FLASH as a treatment technique.