PAUL SCHERRER INSTITUT

SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #20_08/2020

Dear Reader,

In this edition, the clinical results of the management of ACCs of the Head and Neck (H&N) region, treated with Pencil Beam Scanning (PBS) proton therapy, are presented. This is an important analysis on H&N cancers, which is a growing indication for protons. Thirty-five ACC patients were managed by PSI and only a minority (11%) of them received concomitant chemotherapy. Thirteen disease-progressions were observed, mostly distantly. On univariate analysis, the risk of local failure was affected by patient's age and a significant difference was observed between median age of patients who progressed locally as opposed to those with distant metastasis. The overall 2-year local tumor control was excellent (i.e. >92%) and these preliminary results are in line with those published by other groups showing good clinical outcome for ACC patients treated with protons, suggesting that these patients do not need to be sent routinely abroad to a carbon ion center.

The report of another analysis on the robustness of PBS proton therapy, delivered for skull base tumors, is also detailed in this issue. Twenty-two % of PSI's skull base tumor cohort presented with a local recurrence and treatment-robustness was evaluated retrospectively for these cases in terms of setup and range uncertainties. Error bar distributions were generated using the 'worst case' scenario approach. Using an isotropic PTV extension paradigm is valid, as this analysis did not show any correlation between lack of robustness and local failure, as displayed in Fig 2. It is however evident from Fig. 1, that the main driver of local failure are dosimetric parameters, resulting from dose-constraints determined by the OARs in direct vicinity of the target volumes. The main exciting news is however the details of the ultra-high FLASH dose rate performed with Gantry 1, reaching up to 9000 Gy/s in a single spot! The above picture displays the 'messy' non-clinical environment of this research unit for these experiments on Zebra fish eggs. I take the opportunity to thanks again the Radiobiology team from the CHUV, Lausanne, led by Dr Marie-Catherine Vozenin, who helped us setting up these experiments. As this edition will be released, a new set of experiments are scheduled to deliver 1, 100 and 1000 Gy/s to biological samples. It remains to be seen if FLASH will indeed live to clinicians' expectations but the first experiments on bone mets patients are now scheduled to start in the US under the IDE (Investigational Device Exception) from the FDA obtained by Varian Medical Systems. Let us keep our fingers crossed that FLASH will indeed optimize clinical results for patients undergoing radiation treatments. That being said, I wish all of you all the best in these challenging times.

Yours sincerely,
Prof. Damien Charles Weber,
Chairman of CPT
Paul Scherrer Institute

Radio-Oncology News

Clinical outcomes of pencil beam-scanning proton therapy in head and neck adenoid cystic carcinoma

Background

Adenoid cystic carcinoma (ACC) is a rare tumor of the minor and major salivary glands. It typically features extensive local infiltration into the adjacent tissues and, regionally, along the neural fibers rather than into the local lymph nodes. Its treatment requires – if possible – a complete surgical resection and in vast majority of cases an adjuvant irradiation. Proton therapy (PT), in particular utilizing the advanced pencil-beam scanning (PBS) delivery technique uses thousands of millimeter-thin single beams which deposit their peak energy at a precisely set depth in tissue. Dosimetrically, this results in significantly reduced relative entry dose and no exit dose of each whole beam, enabling an exceptionally conformal dose distribution. A high chance of achieving local tumor control while maintaining an acceptable toxicity profile can be therefore expected clinically. In the present study we report the outcome of patients treated with PBS PT for ACCs.

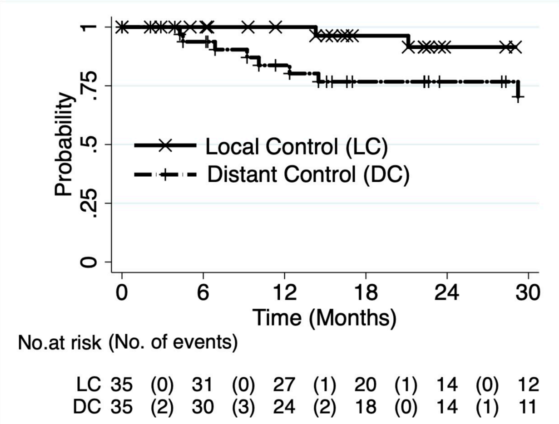


Figure 1: Curves demonstrating the 2-year local and distant control of ACC patients treated with proton therapy.

Materials & Methods

Adult patients (> 18 years) with newly diagnosed ACC of the head and neck treated at our institution with PBS PT were included in this analysis, except if they had metastatic disease, Karnofsky Performance status < 80% and if they underwent prior irradiation. All 35 patients, treated between 2001 and 2017, were immobilized in supine treatment position. Delineation of target volumes and organs at risk (OAR) were done on a 3D high resolution planning CT fused with pre- and postoperative MRIs. Treatment planning was performed using an in-house developed planning software according to the ICRU 62 and 83 guidelines and also approved on an internal review board.

Results

The median patient age was 45.4 years (range: 27.8 - 81.3). Prior to PT, 26 patients (74.3%) underwent surgery with R0/R1/R2 outcome in 5, 13 and 8 cases, respectively. Nine patients presented with inoperable disease and underwent biopsy only. Four (11.4%) patients received concomitant chemotherapy. 19 male and 16 female patients received median doses of 70 and 75.6 GyRBE for postoperative and standalone irradiations, respectively. Overall, the PT was well tolerated by the patients. Five patients (14.2%) experienced grade 3 acute toxicity.
The median follow-up was 30 months (range: 3.7 – 202.8). During the follow-up time, 13 (37.1%) patients experienced disease progression, which included 4 patients with local failures, 6 with distant metastasis as well as both distant and local progression in 3 cases (in all of these the distant metastases occurred first). The estimated 2-year local control (LC), distant control, progression free survival (PFS) and overall survival (OS) was 92.2%, 77.8%, 74.3% and 88.8%, respectively. In univariate analysis, the risk of local failure was affected by patient age with a cutoff of 63 years (risk >63: 55.6% vs. ≤63: 7.7%; p= 0.002). A significant difference was observed between median age of patients who progressed locally and those with distant metastasis (61.3 vs 42.3 years; p = 0.005). The only factor predicting the risk of progression was the tumor T stage (T4a-c: 50% vs T1-3 combined: 9.1%; p=0.045). Significant predictors of the risk of death were the tumor prognostic group (IVB-IVC: 50%, IV-IVA: 7.7%, other stages: 0%; p = 0.049) and the tumor T stage (T4a-c: 20.8% vs. all other stages: 0%; p = 0.032). Two patients (6.1%) developed 3 grade 3 late toxicities observed at a median of 22.3 months. No grade 4 or 5 toxicities were observed.

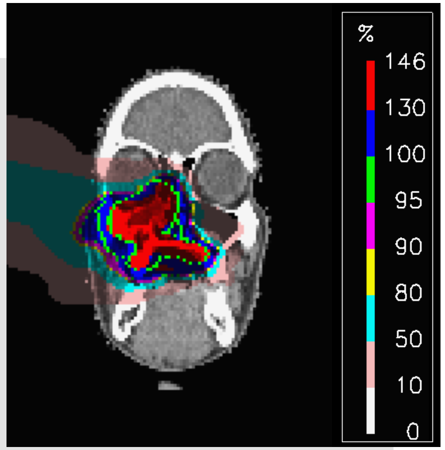


Figure 2: Dose distribution of a simultaneous integrated boost (SIB) plan for a 37-year old male patient with ACC of the left hard palate with perineural infiltration (coronal view). Two dose levels were applied: 70.8 GyRBE to the high risk region (red color ~ 130% dose) and 54 GyRBE to the intermediate risk region (blue color ~ 100% dose). The contralateral side could be completely spared.

Conclusions

PBS PT is a safe and effective way of delivering curative irradiation in high doses required for ACC patients. Distant metastases are the main pattern of failure. Our data suggests that age, tumor stage and clinical stage had a significant negative impact on LC, OS and PFS.

The results of this study were published recently (Pelak et al. Clinical outcomes of head and neck adenoid cystic carcinoma patients treated with pencil beam-scanning proton therapy; Oral Oncology).

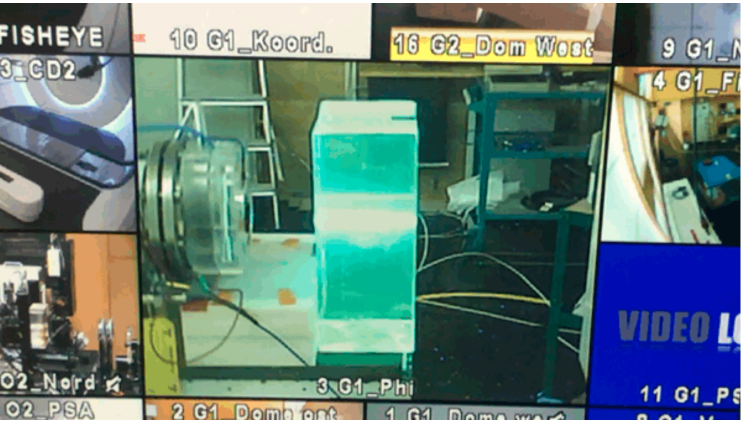
Medical-Physics News

Gantry 1 at PSI commissioned for FLASH research with protons

Introduction

In recent years, several studies have indicated that ultra-high dose rates might result in reduced toxicities to healthy tissues while keeping at least the same tumor control as in the case of treatments with standard dose rate levels (so-called FLASH effect). The topic has gained international attention and many leading centers for radiation oncology have launched their research programs on the FLASH effect. In Switzerland, a leading role in the international research of FLASH has been played by the Lausanne University Hospital (CHUV). They commissioned a prototype linac for FLASH radiotherapy with electrons, which has already been used to perform the first ever FLASH treatment of a human patient in 2018.

The FLASH effect has become interesting also for the proton therapy community. Several centers in the world, as well as main vendors in the field, started to investigate the possibility of reaching FLASH dose rates with existing machines. Based on the studies with photons and electrons, it has been concluded that the threshold for the FLASH effect is at least 40 Gy/s, at least a factor 10 higher than conventional dose rates. However, the definition of the dose rate is prone to ambiguities, as the beam has its microstructure and the average dose rate may be substantially different from the maximum dose rate in a short pulse. The definition of the dose rate is also difficult for pencil beam scanning, as it has a sequential character. Since the mechanism of FLASH has not been fully explained, a potential influence of pauses in dose delivery and fractionation is not understood yet. Therefore, exact conditions for the FLASH effect to occur remain unknown and represent a topic of numerous studies. Thus, flexible FLASH test benches, able to provide different dose rates and irradiation conditions, are required.

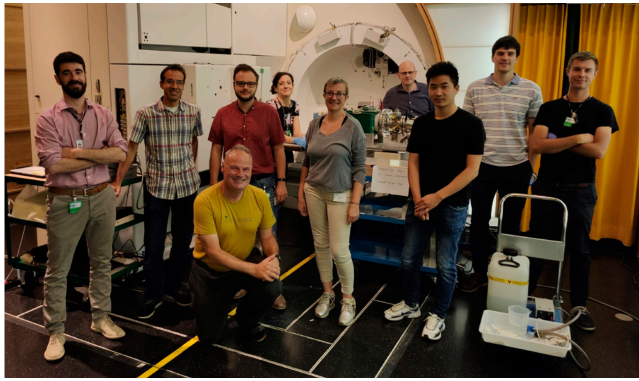


Figur 1: Live image from a video camera of a 525 nA proton beam traversing a scintillating block. The length of the pulse was 10 ms.

Gantry 1 at PSI – a perfect tool for FLASH research

Gantry 1 treated patients from 1996 until the end of 2018. It was the first facility worldwide that used the spot-scanning technique. It is also equipped with a fully automated, discretized range shifter mounted on the gantry nozzle. This feature gives a unique opportunity to transport an un-degraded proton beam to the isocenter in order to maximize the beam intensity, hence the dose rate, while keeping the possibility of conformal (Bragg peak) irradiations. As such, this gantry is an ideal FLASH test bench for protons.

In the past few months, we have implemented all the necessary modifications to enable FLASH irradiations at Gantry 1. Safety requirements were first defined and the existing safety systems of the gantry have been adapted accordingly. We optimized the beamline parameters to transport a 250 MeV produced by the PSI COMET cyclotron to the treatment room with minimum loses, achieving a transmission of up to 85% and a beam current of 680 nA at the isocenter. One of the first irradiations in the FLASH mode is visualized in Fig. 1. To control the dose in the FLASH regime, we characterized and calibrated a dose monitor on the gantry against a dose-rate independent measurement (Faraday cup) together with a redundant measurement using a commercial ionization chamber. With these solutions, we reached an absolute dose accuracy of 2-3% for a wide dose rate spectrum from 1 to 9000 Gy/s in a single spot in water. For single pencil beams, different dose rates can also be achieved by varying the number of range shifter plates and thus the spot size. With our set-up, dose rates of up to 9000Gy/s along the central axis have been achieved for a spot of 2 mm (1 sigma).



Figur 2: Team of researchers from PSI and CHUV at Gantry 1 during the first biological FLASH experiment

Biological experiments

After the successful commissioning of the gantry for FLASH irradiations, we have launched an experimental program together with our partners from the Lausanne University Hospital (CHUV) and Varian. As such, we are currently conducting experiments with zebrafish embryos together with the team of Marie-Catherine Vozenin from CHUV (Fig. 2) in order to quantify any FLASH effects in biological samples.

This work has been presented at the virtual annual meeting of the American Association of Physics in Medicine (AAPM) mid July 2020.

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Medical-Physics News

Is there a correlation between robustness and tumor control for skull base proton PBS treatments?

Introduction

The most modern technique for delivering protons is pencil beam scanning (PBS). With proton therapy, highly conformal dose distributions can be delivered to the target volume, while OARs situated in the proximity can be spared. However, due to the physical characteristics of PT, there is a general worry in the radiotherapy community that the resulting dose distributions might be substantially affected by both range and set-up uncertainties.
Range uncertainties are generally systematic and propagate through the course of the therapy, whereas setup uncertainties tend to be randomly distributed through the therapy, and therefore their importance is reduced. The "robustness" of a treatment plan depends on the sensitivity to these uncertainties. If the uncertainties are low, the plan can be considered "robust".
Skull base Chordomas (Ch) and Chondrosarcomas (ChSa) are major indications of proton therapy at our institute. These are tumors whose management is challenging because they are situated in close vicinity to a number of critical structures, like the brainstem and the anterior optic pathways. Due to the well-defined range of protons, highly conformal dose distribution to such tumours can be delivered while sparing neighboring critical structures. However, how robust are these plans to delivery uncertainties, and could problems with robustness affect treatment outcomes?

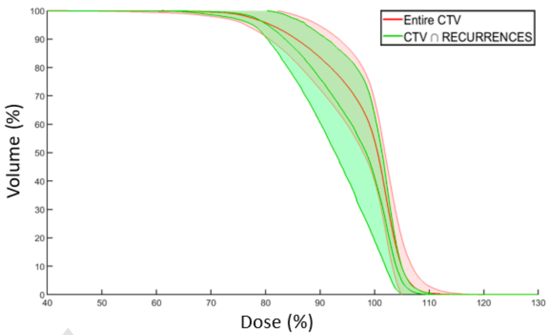

Figure 1: The plots represent the mean and standard deviation of all DVHs for the targets and the onset of recurrences.

Methods and Materials

Between 2003 and 2017, 222 patients with skull-base chondrosarcomas and Chordomas were treated with PBS PT at PSI, to a median total dose of 70 GyRBE and 74 GyRBE respectively. All plans were optimized on a 5mm isotropical expansion of the CTV using our in-house developed treatment planning system. No additional range adapted PTV's or robust optimisation were used. Follow-up MRIs were systematically acquired on all patients, and local failures (LFs) identified and contoured in 49 (22%) patients. For all cases, treatment robustness to both set-up (±1.76 mm for bite-block and ±2.25 mm for mask considering confidence interval of 85%) and range (±3%) were retrospectively computed, and error bar distributions generated using the 'worst case scenario' approach. Finally, dosimetric and robustness parameters in the form of Dose Volume Histograms (DVH) and Error Volume Histograms (EVH) were computed for both the full CTV, as well as the union of the recurrence volume and CTV, for all cases.

Results

The spread of DVHs and EVHs for all cases for the entire CTV (red) and just the regions of recurrence overlapping with the CTV (green) are shown in fig. 1 and fig 2, respectively. No correlation was found between LF and robustness either for the whole CTV or for the overlapping regions of recurrence (fig. 2). Indeed, dose robustness has been found to be generally better (EVH shifted to the bottom left) in the recurrence region compared to the whole CTV (fig. 2). A minor, but statistically insignificant correlation was however found as a function of nominal dose, with the mean dose to the GTV and CTV being slightly lower (95% compared to 98%) for patients with LF (fig. 1).

Conclusions

Our results for skull base tumors show that there is no correlation of LF to lack of robustness, indicating that the use of a simple, isotropic PTV is an effective approach for dealing with treatment uncertainties for these patients. On the other hand, the analysis of dosimetric parameters seems to indicate that the dosimetric quality of the nominal plan is most important for obtaining tumor control.

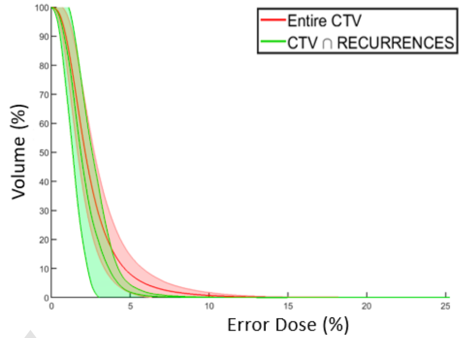

Figure 2: The plots represent the mean and standard deviation of all EVHs for the targets and the onset of recurrences.

This work will be presented at this year's ESTRO conference in late fall in Vienna, Austria.

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