SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #26_08/2022

Dear Reader,

Welcome to this second 2022 SpotON+ Newsletter published during this extremely hot summer. In this edition, Dr Bachmann reports on the outcome of patients (median age, 32 years) with either malignant or benign peripheral nerve sheath tumors (PNSTs) treated with pencil beam scanning proton therapy. These tumors are usually difficult to treat (especially if malignant due to the high-radiation dose needed to control them) as they are stemming from nervous structures (or more precisely from the thin connective tissue sheaths or endoneuria wrapping the axons) and are located usually in direct vicinity of uninvolved nerves and/or spinal cord. Most (78%) of these tumors in our series were treated upfront at diagnosis and NF-1 disease was present in roughly 1 patient out of 5 patients. Local failure was only observed in 8 patients, the majority of them (88%) presenting with malignant as opposed to benign PNST. One of the main issue with mPNSTs is the distant failure rate (in our series, the 2-year distant control was 61%) and on univariate analysis distant failure was significantly associated with higher FNCLCC grade and with the extent of tumor resection. No grade ≥ 3 late toxicity was observed (late toxicity rates were similar with NF-1 and non NF-1 patients in this small series). The delivery of high dose proton radiation seems thus to be effective to locally control the tumor and was associated with a low rate of acute and late toxicity. In the second article, Francesca Albertini reports on the RAPTOR European project (Horizon Europe 2020, No 955956) which has PSI as a lead house. Adaptive treatments are even more critical in proton therapy than photon therapy for many reasons not limited but including issues with the range of protons, the so-called range uncertainty. Adapting treatment to anatomical changes, tumor response and change in patient positioning is critical when utilizing protons therapeutically. More information can be heard on our research podcast. This project involves many academic and commercial partners and will undoubtedly lead to a number of research outputs that could be critical for this plan-adaptation paradigm. Finally, the last article explores another way to increase the therapeutic ratio by using nanoparticles to amplify the cellular damage resulting from proton radiation. This important work resulted from the collaborative endeavor with Prof. Inge Hermann and her team from EMPA. In a cellular model, nanoparticles associated with transmission proton therapy increased the production of reactive oxygen species (ROS) which are the main driver for (indirect) radiation-induced DNA damage. One particular nanoparticle (TiO2) did induce the production of ROS under the experimental condition utilizing protons. It will be interesting to assess if the same observed effect (i.e. increase in ROS production) would be also observed in several localizations of the Bragg peaks with consequentially different LETs. We are planning to further pursue this critical research with EMPA within the framework of a new grant.

That being said, I hope that this newsletter was of interest to you and I stay tuned for the next edition in 4 months' time, which will bring us a cooler temperature and 'normal' feeling season.

Sincerely,

Prof. Damien C. Weber,
Chairman Center for Proton Therapy,
Paul Scherrer Institute

Radio-Oncology News

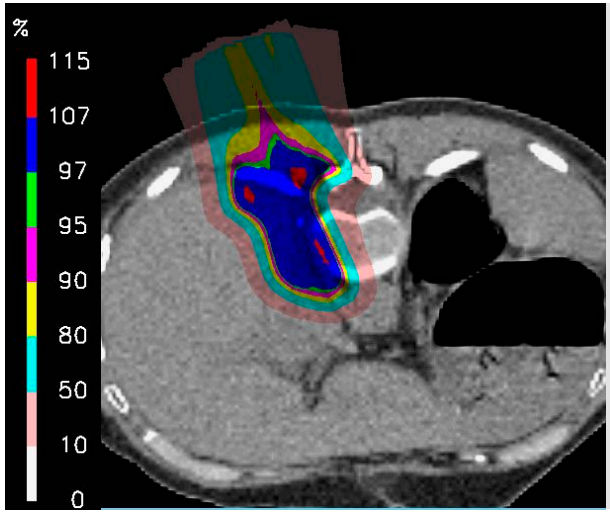
Clinical outcome after pencil beam scanning proton therapy of patients with non-metastatic malignant and benign peripheral nerve sheath tumors

Background

Peripheral nerve sheath tumors (PNSTs) commonly arise from peripheral nerve roots and grow locally invasive. Malignant PNSTs (mPNSTs) represent aggressive sarcomas of neural origin that can originate from PNSTs. Radiation therapy is commonly used as part of the required multimodal treatment. However, both entities tend to occur early in life and are associated with the genetic disorder neurofibromatosis type 1 (NF-1), which is known to cause increased radiosensitivity. Pencil beam scanning proton therapy (PBSPT) allows for a minimization of dose delivered to organs at risk and the integral dose and, thus, potentially also a reduction of radiation-induced adverse events. We report the clinical outcome and toxicity rates of patients with (m)PNSTs treated with PBSPT.

Methods

We retrospectively reviewed 36 patients who received PBSPT (median dose, 64 Gy_{RBE}) with curative intent for (m)PNSTs between 1999 and 2020 at our institute. Twenty-eight (78%) and 8 (22%) patients were treated at diagnosis and for tumor recurrence/progression, respectively. Median age was 32 years (range, 3 – 75). mPNST and PNST were diagnosed in 31 (86%) and 5 (14%) patients, respectively. Underlying NF-1 disease was found in 8 (22%) patients. Histological workup of mPNSTs after complete resection (R0, n=11, 31%) or partial resection (R1/R2 or biopsy, n=15, 42%) showed a FNCLCC (*Fédération Nationale des Centres de Lutte Contre Le Cancer*) Grade 1, 2 and 3 in 2 (6%), 14 (39%) and 10 (28%) cases, respectively. Acute and late toxicities were recorded according to CTCAE v4.1. Overall survival (OS), local control (LC), and distant control (DC) were estimated using the Kaplan-Meier method. Univariate Cox regression was used to investigate prognostic factors for local failure, distant failure and OS.



Dose distribution of an adjuvant pencil beam scanning proton therapy plan for a 57-year old woman with a malignant peripheral nerve sheath tumour in the right retroperitoneum (axial view) after undergoing neoadjuvant irradiation with photons (50 Gy) and R1 resection. A total dose of 50 Gy(RBE) was delivered in 25 fractions in the area of R1 resection. The spinal cord, bowel and liver were effectively spared. Treatment was well tolerated without relevant side effects. There is no evidence of recurrent disease 3 years after PBSPT.

Results

After a median follow-up time of 31 months (range, 4 – 194), local failure was observed in 8 (22%; 1 PNST and 7 mPNST) patients, with 6 failures being classified as “in-field” and 2 as “marginal” failures. Fourteen (39%) patients experienced distant failure and 13 (36%) patients died with progressive disease. Estimated 2-year OS, LC and DC was 75.5%, 73.5% and 61.2%, respectively. Univariate analysis showed a significant negative association between distant failure and higher FNCLCC grade (HR 3.79, p=0.013) and R2/RX resection status (HR 3.97, p=0.035). These two factors demonstrate a similar impact on survival: 2-year survival rate for patients with FNCLCC grade 3 tumors and R2/RX resection status was 67.5% and 59.8%, while FNCLCC grade ≤2 tumors and R0/R1 resection status had a 2-year survival rate of 78.7% and 93.3%, respectively. Additionally, on univariate analysis lower performance score (KPS/Lansky ≤80) was significantly associated with increased distant failure and patients with larger tumors (>5cm) showed a trend toward an increased risk for distant failure and worse survival. NF-1 patients had similar failure and survival rates as non-NF-1 patients. No prognostic factor for local failure was identifiable.

Acute grade 3 toxicity (dermatitis, mucositis, pain) was observed in 5 (14%) patients. Late grade 3 cataract and osteonecrosis were both observed in 1 (3%) patient, 34 and 194 months after PBSPT, respectively. There was no late grade >3 toxicity or radiation-induced secondary cancer. The rates of any grade ≥3 acute toxicity and any late toxicity in NF-1 patients were statistically similar compared to non-NF-1 patients.

Conclusion

To our knowledge, this is the first study to analyze the outcome of (m)PNSTs treated with proton therapy using a PBS delivery paradigm. In our cohort, consisting mainly of patients with mPNSTs, we report favorable oncological outcomes and low toxicity rates after PBSPT.

This study has recently been published (Bachmann et al. 2022).

Medical-Physics News

RAPTOR – Real-time adaptive particle therapy of cancer

RAPTOR Wall of Fame

To widen the therapeutic window in the era of precision medicine, technology-driven improvements in both advanced image guidance and particle therapy will become indispensable for further improving the quality and effectiveness of radiation therapy. Both techniques are capable of reducing treatment margins and therefore can also reduce the volume of normal tissue irradiated outside the target volume, enabling a safer and more effective delivery of higher dose-per-fraction paradigms.

On-line adaptive proton therapy perfectly combines both aspects. The need of adaptive therapy has been the subject of research at PSI for a number of years. And recently, all the key elements to support an online adaptation for patients treated in the presence of no (or limited deformation) have been developed (sponsored by an SNF-Grant No. 320030_165961: Towards the Daily Adaptive Proton Therapy (DAPT) at PSI), and are currently being implemented in the clinic [Research Podcast].

Last year, the importance of online adaptive proton therapy was also recognised by the European Commission, through their funding of the Real-time Adaptive Particle Therapy Of CanceR (RAPTOR) project, coordinated at PSI. The RAPTOR project brings together multiple proton and particle institutes and industrial partners with the goal of enabling the translation of online adaptive therapy into the clinic. In 2021, 15 fully funded PhD positions were awarded as a European Union's Horizon 2020 Marie Skłodowska-Curie Action (MSCA) Innovative Training Network (ITN). These projects, hosted by 13 beneficiaries all over Europe, aim to improve three main areas of the treatment adaptation process: imaging, daily- intervention and verification.

The 4-year long ITN-RAPTOR project has started on the 1st March 2021 and the first year focused mainly on the implementation of the collaboration strategy and recruitment of the 15 PhD students (see Wall of Fame).

One goal of the RAPTOR project is to educate a new generation of medical physicists to become experts in providing solutions to one of the biggest challenges of particle therapy, i.e. the detrimental effects of anatomical changes. As such, regular training schools are organized during the course of the project, with a special focus on adaptive therapy. The 1st school conducted online in December 2021 was very well perceived. The high-level lectures attracted more than 50 external participants in addition to the RAPTOR PhD students. The 2nd school is already scheduled for September 2022 in Ljubljana whereas the 3rd school is planned to be hosted at PSI in September 2023.

Despite the fact that the PhD students have just recently started working on the RAPTOR project, their scientific value have already been recognized internationally. Andreas Smolders, from PSI, has received the Audience Award for the best oral presentation he gave at the WBIR workshop in Munich, about an unsupervised deep learning method he developed to quantify the uncertainty associated with the output of deformable image registration (DIR) algorithms. Two contributions were also presented at this year's PTCOG60 in Miami. Nadine Vatterodt, from Aarhus, presented the results of a pilot study she initiated to explore the potential of including anatomical error scenarios to account for changes in nasal cavity filling in robust optimization for sinonasal cancer, and Beatrice Foglia, from LMU (Munich), had a poster comparing strategies of dose reconstruction from prompt-gamma radiation in proton therapy.

In the upcoming months, more work from the RAPTOR students will be presented at national and international conferences. To mention only the contribution to the upcoming Swiss meetings, Andreas Smolders and Evangelia Choulilitsa will be presenting an interesting approach on how to improve the accuracy of daily auto-segmented contours and on how to predict the accumulated treatment dose, at the SASRO and at the SSRMP, respectively.

The RAPTOR project can be followed on these social media:

Twitter LinkedIn Instagram

RAPTOR project has received funding from the European Union's Horizon 2020 Marie Skłodowska-Curie Actions under Grant Agreement No. 955956.

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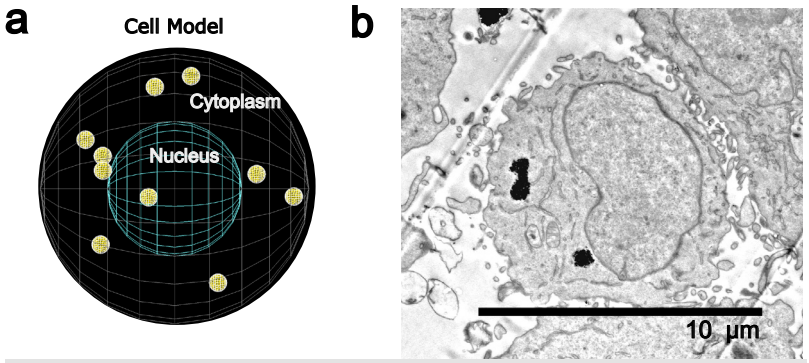
Physics News

Nanotechnology offers a route to amplifying proton treatment of tumors

Proton therapy has been developed to provide oncologists with a new opportunity to spare radiation damage in non-tumorous regions, thanks to the better dose-conformation of protons over photons. Nevertheless, for many treatments (late) toxicity can still be a significant issue. To increase the therapeutic ratio even further, nanotechnology might offer a promising strategy. In an ideal situation, nanoparticles shall be delivered to the tumor and amplify the damage of proton therapy locally.

The idea to use nanoparticles to amplify ionizing irradiation has been developed mainly from the fact that high dense materials, such as metals, can absorb much more radiation than low dense materials such as soft tissue or water, due to the photoelectric effect scaling roughly with the cubed atomic number. Therefore, it has been proposed to incorporate nanoparticles with high atomic numbers into tumor tissues which could then increase the interaction of the tumor with ionizing radiation. The attenuation effect has been described very well for photon beams, where, in case of an ionizing particle-with-nanoparticle interaction, secondary species (such as (Auger) electrons) are emitted from the nanoparticles causing additional damage in the close vicinity. To study and calculate this "physical amplification" effect computational models can be built to represent as-close-as-possible real-life scenarios, while testing different metal and metal oxide nanoparticles.



Geometrical cell model to study the interaction between ionizing radiation and cancer cells that have taken up nanoparticles in small agglomerates with Monte Carlo simulations (a). The cell model consists of the cytoplasm, a central nucleus and a few spherical vesicles, that contain several yellow nanoparticles. The cell model was motivated by the biological "real-life" experimental scenario, as found in transmission electron microscopy (TEM) images of HT1080 cancer cells with taken up HfO_2 nanoparticles (b). Figure adapted with permission from Gerken et al. 2022.

Despite expectations that such a physical amplification would be insignificant for proton beam, a second, "chemical amplification" effect has been observed during the proton/photon irradiation of nanoparticle solutions. In proton transmission irradiations performed at PSI Gantry 2, we have found that nanoparticles enhance the production of reactive oxygen species (ROS), which are the main driver of indirect DNA radiation damage causing 50-90% of cancer treatment damage. We were able to show that mainly hydroxyl radicals (one of the ROS species) are responsible for the nanoparticle enhanced radiation damage in cells, and that TiO_2 nanoparticles can amplify the production of ROS very effectively also under proton irradiation. The responsible mechanism is the excitation of the TiO_2 nanoparticle during the bombardment with protons leading to charge separations and the occurrence of electrons and electron holes on the surface of the nanoparticle. These charges then catalyze the production of ROS on the nanoparticle surface leading to a locally amplified proton therapy damage. Investigation with proton beams are still ongoing; we speculate that additional processes such as nuclear reactions could be involved in the amplification of the proton radiation damage. Future experiments in different scenarios (e.g., different LET) could still provide new insights on this interesting phenomenon.

With the current progress of nanotechnology and nanomaterial designs, exciting opportunities are emerging to amplify proton therapy. For clinical advancement and in order to have a societal impact, it is of great importance in further studies to find out which material designs are the most beneficial for proton therapy enhancement while keeping in mind that such materials can be produced on industrial scale.

This work has been a collaboration between the Centre for Proton Therapy, the Nanoparticle Systems Engineering Laboratory of ETHZ, as well as EMPA and the Cantonal Hospital St. Gallen, and has recently been published (Gerken et al. 2022).

Imprint

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Villigen PSI, August 2022