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PSI

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SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #18_10/2019

Dear Reader,

I am happy to report that the Proton Therapy symposium, held during SASRO, attracted a substantial number of colleagues, which shows the interest of the radiation oncology community for this treatment modality. You find in this edition summaries of the talks. PSI is the only proton therapy center in Switzerland as probably everyone knows. What is failing unfortunately is a national strategy for this treatment modality in our fragmented healthcare system that will define the needs of the Swiss population for protons in the future. We can testify that PSI, with key stakeholders (University Hospitals, SRO, HSM etc...), advocated to have such a strategy and have a white paper done at a the Federal Office of Public Health's (FOPH) meeting in Bern, December 2016; the FOPH has shown so far probably insufficient leadership and proactive guidance for proton therapy. PSI has seeked from the FOPH the assessment of a phase III trial for lung cancer in Switzerland, performed within the framework of a multi-centric study. The response from BAG is eagerly awaited, as the generation of high quality clinical data is of paramount importance for the community. As discussed during the symposium, this topic was debated also within the European Particle Therapy Network (EPTN; https://www.estro.org/Science/EPTN) on an international level and it was unanimously agreed that such a clinical endeavor was important to steer Proton therapy in the area of evidence-based medicine. This strategy was also discussed at the European Commission –DG Santé, in conjunction with the European Investment Bank, in a closed meeting in October 2018 during which the knowledge gaps in Proton therapy were discussed. The successful completion of prospective studies on the European level will be possible in the not too distant future, as a substantial number of proton centers have or will shortly come on line. A number of trials have been designed for various tumor entities. For head and neck alone, three trials are on the drawing board (TORPEDO, IMPERATOR, DAHANCA 35). Importantly, an European prospective registry will be launched Q4 2019 within the framework on the EORTC-ESTRO E2-RADIatE (EORTC 18033) project. Proton therapy definitively suffers from a lack of collective knowledge on how treatments affect patient's survival and quality of life for a number of 'niche' cancers. As such, the ESTRO-EORTC has decided to launch a platform built to host prospective data registries (i.e. ParticleCARE) of "real-world" data on patients treated with protons. PSI is currently discussing with its clinical partners on how to bridge the gap between the photon and proton world within our community and how to refer swiftly a patient to our center with a participative-management paradigm. A first meeting is scheduled by the end of this year.

That being said, I wish you a good start after the warm summer recess. Please stay tuned for our next edition of our newsletter for some results stemming from our ongoing clinical/research program.

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

Indications for protons

Presented by Dr. Marc Walser, Senior Radiation Oncologist

Indications for proton therapy in Switzerland are entity based. The Federal Office of Public Health FOPH has accepted the application by PSI on certain indications in 2009. For the following diagnoses proton therapy is reimbursed by the compulsory health insurance:

- Intraocular Melanomas
- Tumors of the skull/skull base:
  - Chordoma
  - Chondrosarcoma
  - Head&Neck-Cancer (e.g. SCC, Adeno-CA, ACC, Esthesioneuroblastoma)
- Tumors of brain and meninges
  - Low grade gliomas
  - Meningiomas
- Tumors outside skull along the vertebral column, trunk and extremities
  - Sarcomas
- Pediatric tumors

So far, almost 7'500 patients with ocular tumors have been successfully treated at PSI since 1984 which represents 20 % of all patients with ocular tumors treated with protons worldwide.

Chordomas and Chondrosarcomas are very rare tumors, but one of the standard diagnoses treated with protons at PSI. Our long-standing experience has been described in numerous publications [Weber 2018; Weber 2016; Weber 2016b; Snider 2018].

Meningiomas usually grow slowly and do not metastasize, but can cause severe local problems. Over 160 meningioma patients have been treated with protons at PSI, the majority of them belong to the benign, grade I category. A recent publication shows a 5-year local control rate of 86% and a 5-year high grade toxicity free survival of 89% [Murray 2017].

Sarcomas are malignant cancers of the connective and supportive tissues. They can develop in all regions of the body and require a high irradiation dose to achieve local control. With protons the dose to surrounding healthy tissue can be minimized which reduces toxicity. In close collaboration with the Kantonsspital Aarau, a clinical study of concurrent hyperthermia and proton beam radiotherapy in primary and recurrent unresectable soft tissue sarcoma is running and open for patient enrollment [HYPROSAR].

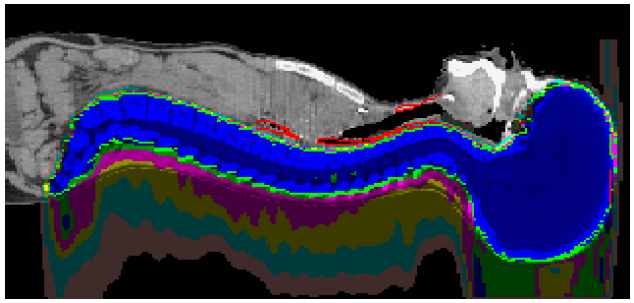


Figure 2: dosimetry of a pediatric patient with medulloblastoma, treated with cranio-spinal axis irradiation and a boost to the brain.

Luckily, cancer disease is very rare in children. Based on multi-disciplinary treatment concepts the overall survival of pediatric oncological patients have considerably improved. However, the therapy induced side effects can be substantial with a life-long negative impact on the quality of life. Proton therapy is reimbursed by the health insurance for all types of pediatric tumors. Over 550 children have been treated with protons at PSI with the aim of reducing long-term toxicity and minimizing the low dose bath to prevent secondary malignancies. Most common diagnoses are ependymoma [Ares 2016], rhabdomyosarcoma [Leiser 2016], medulloblastoma and Ewing sarcoma [Weber 2017]. Due to the close collaboration with the children's hospital in Zürich, also very small children can benefit from proton irradiation under anesthesia.

In very exceptional cases the indication for proton therapy outside the list of FOPH can be discussed individually based on a clear dosimetric advantage of protons. Applications for new indications to the FOPH in order to be added to the approved list have to be justified based on randomized trial data. As the necessary number of patients cannot be recruited in Switzerland only, we are happy to have successfully joined the American NRG oncology network as an associate member. This gives us the possibility to participate in international clinical trials and help to extend the requested level I evidence for proton therapy. Our aim is to join the RTOG 1308 non-small cell lung cancer randomized trial (photons vs. protons) next year.

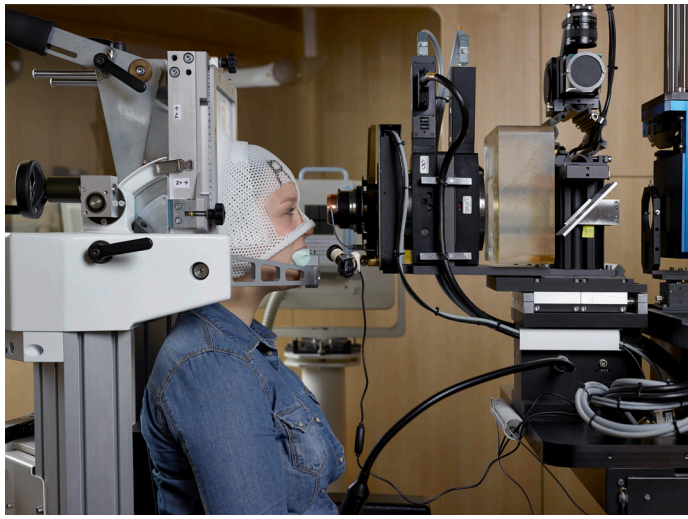


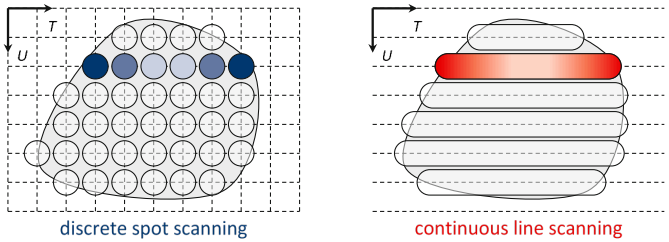
Figure 1: patient immobilized in treatment position for eye irradiation in OPTIS 2 treatment room.

Advanced delivery

Presented by Dr. David Meer, Senior Scientist Technology Development

PSI has been influencing the field of radiation oncology by using particle therapy for almost 40 years. Technological innovations have always played a key role. The Piotron, the technologically most advanced facility for irradiations with pions, was already in clinical operation from 1980 to 1993. The OPTIS facility for the treatment of eye tumours, which started in the mid-1980s, was one of the first facilities in Europe using protons to treat tumours. With the development of the spot scanning technique, which was used clinically on Gantry 1 for the first time in 1996, Intensity Modulated Proton Therapy (IMPT) could be delivered, which was unique worldwide for more than a decade. With the commissioning of the first superconducting cyclotron, PSI has also impacted the field of accelerators.

Gantry 2, which went into clinical operation in 2013, is still setting standards. These include fast energy modulation, parallel scanning or automated operation with a pre-absorber. The acceleration of the dose application and the increase of robustness for moving targets are two of the main focuses of the current technological development on Gantry 2. Last year, for example, an irradiation mode was put into operation which can adapt the beam current from the accelerator spot by spot and thus precisely irradiate spots with very low doses if needed. In order to perform repeated dose deliveries – so-called re-scanning – more efficiently, the dose is also delivered during the reversed energy sequence. As no full ramping of the beam line is required, the irradiation time can be significantly reduced. Both are techniques that have so far been used only at PSI. Under experimental testing is the so-called line-scanning, in which the dose is delivered instead of discrete spots by continuously scanning over the target volume. This delivery modality will further reduce the irradiation time significantly. Technological development will remain a focus of PSI and we continue to work on innovative therapy concepts for proton therapy.



discrete spot scanning | continuous line scanning

Comparison of two irradiation modalities:
Discrete spot scanning (left, standard delivery method) and continuous line scanning (right, under development).

Medical Physics Research and Development

Presented by Dr. Francesca Albertini, Senior Medical Physicist Development

Research and Development has always been at the core of the Center for Proton Therapy at PSI. As such, our current medical physic research covers the topics as shown below:

P.I.: J. Hrbaccek

Advanced Ocular therapy
- workflow development to support a fully automatized, non-invasive MRI-based only approach and its clinical implementation

S. van de Water

P.I.: S. Safai

Advanced Treatment Modalities
- Flash therapy

P.I.: F. Albertini

Daily Adapted Proton Therapy (DAPT)
- workflow development to support a daily on-line adaptation and its clinical implementation

P.I.= Principal Investigator

P.I: G. Fattori

P.I.: S. Safai

Biological models for treatment planning
- use of functional information to adjust the radiation dose delivery
- use of multi-parametric physiological data to better predict patient outcome

P.I.: Y. Zhang

P.I.: G. Fattori

Motion Mitigation and 4D planning
- gating, rescanning and tracking
- modelling and experimental verification of 4D treatments
- 4D imaging
- 4D dose calculations and optimization
- 4D numerical phantom

Strategic Focus Area
Personalized Health and Related Technologies

FNSNF Swiss National Science Foundation

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As well as being pursued by PSI staff, our research program is strongly supported by post-doctoral, PhD, master and bachelor students from Switzerland and all over the world, as well as being supported by a number of grants and industrial collaborations.

Case study: young woman with Hodgkin Lymphoma

Presented by Alessandra Bolsi, Senior Medical Physisist and Dr. Sébastien Tran, Radiation Oncologist

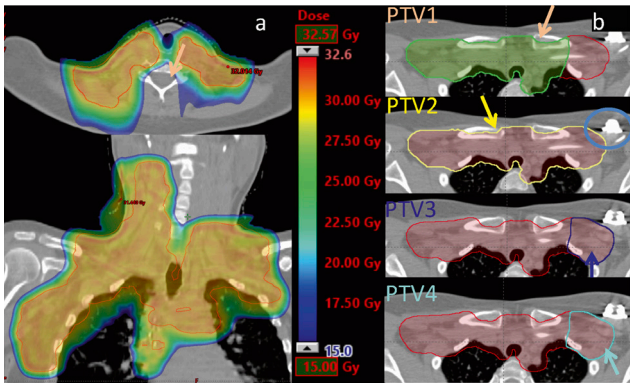

Figure 2: (a) Very conformal dose distribution obtained for this complex lymphoma case. (b) Representation of the 4 fields directions used and of the partial PTVs (PTV1 to PTV4) used in the optimization process. In red the PTV to be treated with 30GyRBE.

Clinical presentation

This 29-year old, otherwise healthy patient consulted due to enlarged right cervical lymph nodes. A PET-CT showed hypermetabolic adenopathies in the right cervical and axillary as well as bilateral supraclavicular and mediastinal regions (Figure 1). A biopsy revealed Hodgkin Lymphoma, nodular sclerosis type. The disease was staged IIA, early unfavorable.

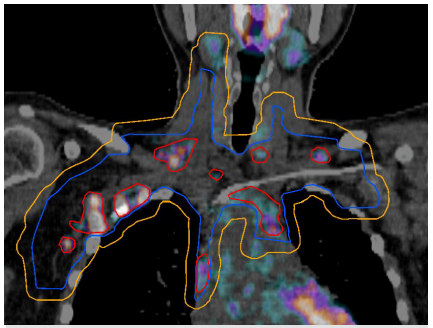

Figure 1: Registration of the planning-CT with the initial PET sequence. Red contour = GTV = initial PET pathological signal. Blue contour = CTV = GTV + 10mm, including involved lymph node stations, corrected for anatomical boundaries. Orange contour = PTV = CTV + 7mm

The patient received 2 cycles of BEACOPP, followed by 2 cycles of ABVD. The interim PET-CT showed a complete metabolic response. Involved-field consolidation irradiation was recommended and the patient was referred to PSI CPT for proton therapy by her treating physicians.

Proton treatment planning

The patient was scanned in a supine position, arms down. The planning-CT was fused with the initial PET-CT. The target volumes delineation concept is illustrated in Figure 1. Breathing motion was assessed with a slow-CT, which did not show any significant motion in the target region. Planning was therefore done with a 3D approach. Dose prescription to the PTV was 30GyRBE in 15 fractions, 1x/day, 5x/week. The defined organs at risks (OAR) included the breast, heart and coronary arteries, which were to be spared as much as reasonably achievable (ALARA). Breast cancer irradiation dose constraints were used for the lungs (D10 ‹ 25 Gy).

Considering the complexity of the target shape, the many OARs, the presence of a metallic port and the potential residual breathing motion, the proton technique that was selected included multiple fields, with different field directions, each targeting a different PTV sub-portion. Each area of the PTV was covered by at least 2 fields. The resulting plan was a single isocenter IMPT plan with 4 fields, 2 anterior slightly oblique and two posterior (one postero-anterior and one slightly oblique). The anterior approach was used for the most cranial part of the PTV down to the level of the breast, whilst posterior approach was privileged for the most caudal portion of the PTV to avoid the breasts and to minimize lung dose. The resulting dose distribution and the field directions are displayed in Figure 2. The plan is very conformal with V95 % target coverage above 99 % for GTV, CTV and PTV. This was obtained whilst minimizing the dose to OARs: average dose to breast glands was below 3 GyRBE [Right: 3.0 ; Left:0.0] and to the full breasts below 4.5 GyRBE [Right: 4.4; Left:0.7]. Mean dose to heart was below 6 GyRBE whilst for both lungs the D10 was below 25.5 Gy RBE for both of them [Right: 25.5; Left: 25.1].

Proton therapy delivery

Pencil Beam scanning irradiation was delivered using CPT's Gantry 3, manufactured by Varian. Adequate positioning was ensured by sets of kV imaging before each field and no set up issue arose during treatment. Proton therapy was completed without interruption or unexpected events. A grade 2 Esophagitis was successfully treated with oral nystatin, pantoprazole and grade 1 analgesics.

Conclusion

We successfully planned and treated this 29 yo patient with a complex treatment target, delivering low doses to key OARs (i.e. heart, breasts), while preserving excellent dose coverage. Proton therapy should therefore be considered in young patients with Lymphoma, especially women, with mediastinal and/or axillary tumor localizations.

Imprint

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