SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #24_12/2021

Dear Reader,

It is my pleasure to introduce you this month's last 2021 Newsletter. You may have seen the recent press release on the first patient with locally advanced (stage III B) NSCLC treated with PBS proton therapy (PT) within the framework of the RTOG 1308 study (clinicaltrial.gov NCT 01993810). This study has been activated by the two NRG centers, namely Kantonspital Aarau and PSI. This female smoker was particularly difficult to treat (delivering 70 GyRBE), as she had extensive nodal involvement (mediastinal and supra clavicular) and the dose-constraints of organs at risk in direct vicinity of the target volume were quite challenging to adhere. But thanks to the conformality of protons, the heart V30% was only 6.5 (dose constraint V30% ‹ 50 in the protocol). Needless to say, treating a mobile tumor with a dynamic beam may lead to under dosage of the primary tumor and/or overshooting of the target. To mitigate the likelihood of this beam/tumor motion interplay effect, we used gated PT (gated window: 30% exhale) with rescanning. The increase of treatment time with rescanning was only 30% in comparison to the non-gated nominal plan.

The target modelling of uveal melanomas by the treatment planning system having the clips information has known limitation and it has always been the goal of PSI to introduce non-invasive imaging techniques to better define the target volume. This work has been published previously but one of our PhD student reports in this issue torsional eye movement detection during patient positioning for proton therapy by measuring the pattern of iris rotations. Twenty consecutive patients were assessed, although one in 5 the evaluation was hindered by the inability of selecting a convenient region of interest in the iris region due to eyelid occlusion or importantly undesired light reflection. For those patients that could be assessed, a good correlation was observed between the BEV x-rays standard images of the clip and the new algorithm.

Lastly, Walser et al. reports the outcome of sacral chordoma patients treated with protons, with (n=10; 17%) or without (n=50; 83%) conventional photon therapy to a median dose of 70 GyRBE, with a fractional dose ranging from 1.8 to 3 Gy RBE. The estimated 4 year local control and overall survival was 77% and 85%, respectively. Not surprinsgly, gross total resection was an independent prognostic factor for tumor control, so was also the tumor extension restricted to bone. Interestingly, there was a suggestion of better tumor local control with hypofractionation (i.e. 3 Gy RBE per fraction), although this did not reach statistical significance. As a result, for large unresected sacral chordoma we propose hypofractionation and may consider hyperthermia as published by Tran et al.

That being said, I hope that this newsletter was of interest to you and I wish all a Merry Christmas and Happy New Year. Hopefully 2022 will easier for the patients, care givers and the general population.

Sincerely,

Prof. Damien C. Weber,

Chairman Center for Proton Therapy,

Paul Scherrer Institute

General

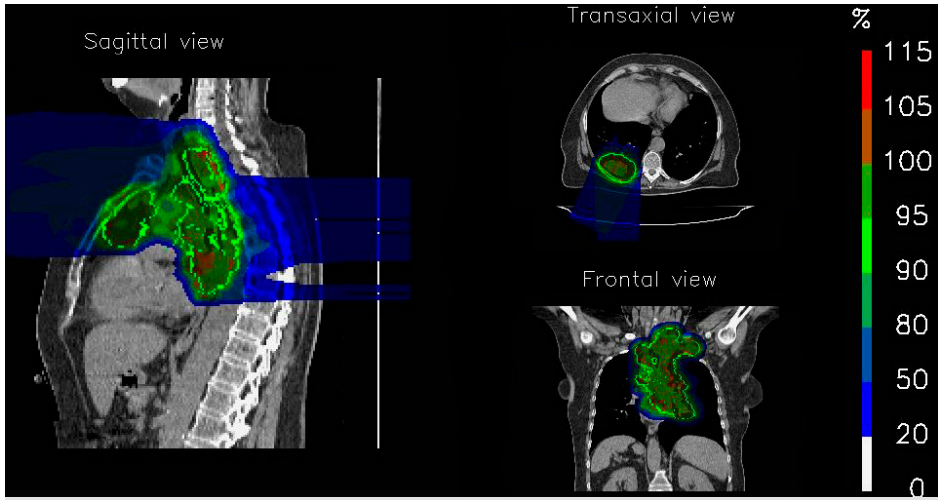
A first for Switzerland: proton therapy to treat lung cancer

Lung cancer is the deadliest type of cancer in Switzerland and also one of the most common: it affects around 4,500 patients every year. Surgery is the most usual form of treatment. In advanced tumours, surgery is followed up with chemotherapy and radiotherapy, and sometimes immunotherapy as well. However, not all tumours can be surgically removed, so scientists are currently conducting intensive research into improving non-invasive treatment methods. For patients in Switzerland, the PSI now offers a novel alternative: proton beam therapy (PBT). While this type of therapy has already become established for treating certain tumours in the area of the head, neck and torso, the treatment of tumours in the lungs is new territory. PSI researchers hope this will extend patient survival rates – even without surgery – and reduce secondary effects caused by radiotherapy, such as heart problems and pneumonitis. Medics expect this much less aggressive but more precise form of radiotherapy will have fewer secondary effects on healthy lung tissue and the heart.

On 9 November a 60-year-old patient suffering from lung cancer received proton beam therapy. The patient had an advanced stage tumour that could not be surgically removed. The 7-week course of irradiation is accompanied by weekly chemotherapy. The treatment is done within the frame of an international randomized clinical trial (title "Phase III randomized trial comparing overall survival after photon versus proton chemoradiotherapy for inoperable stage II-IIIB NSCLC"). The study is led by an US research organisation overseeing oncologic clinical trials, NRG Oncology. PSI is taking part together with the Radio-Oncology Centre of the Cantonal Hospitals of Aarau (KSA) and Baden (KSB) – the only institutes outside the US to do so. The aim of the trial is to compare the outcomes of established radiotherapy with proton therapy in the treatment of non small cell bronchial carcinoma – the most common form of lung cancer – in the advanced, inoperable stage. Primary endpoint is the overall survival (please see detailed study description on clinicaltrial.gov NCT 01993810).

The invitation of both institutions to take part in the trial is chiefly down to their many years of expertise in the field of radiotherapy and the cantonal Radio-Oncology Centre's membership of NRG Oncology. Patients are randomly allocated to either type of treatment: some receive proton therapy at PSI, others radiotherapy at the Radio-Oncology Centre KSA-KSB. Since at the latter for conventional radiotherapy the currently most modern equipment is available, it is fair to describe the study design as to compare the best with the best.

Before the trial could even start, all participating study centers had to go through a lengthy process of accreditation by the M.D. Anderson Cancer Center in Houston, an institute commissioned by NRG Oncology. For data comparison purposes, it is vital to ensure that all patients are treated in the same way and with the same quality standards. To provide the required quality control, for example, the PSI team performed radiotherapy on "phantoms". These dummies have integrated devices for measuring doses and mimic the properties of a human patient.



Dose distribution (70GyRBE) and PTV (green) of the first lung cancer patient

The clinical trial is due to number 330 patients in total, with around 10 of them in Switzerland. The goal is to use both photon and proton therapy to achieve the best possible outcome for the patients.

The patient enrolment phase in Switzerland has just started, so participation in this study is possible. Please contact Dr. Dominc Leiser (dominic.leiser@psi.ch) for further information.

This text is mainly an abridged version of a media release written by Sabine Goldhahn.

Medical-Physics News

Non-invasive recognition of eye torsion through optical imaging of the iris pattern in ocular proton therapy

The introduction of non-invasive imaging techniques such as MRI imaging for treatment planning and optical eye tracking for in-room eye localization could obviate the requirement of surrogate (clips) implantation for patients undergoing ocular proton therapy. This study specifically addresses the issue of torsional eye movement detection during patient positioning. Non-invasive detection of eye torsion is performed by measuring the iris pattern rotations using a beam's eye view optical camera. When handling images of patients to be treated using proton therapy, a number of additional challenges are encountered, such as changing eye position, pupil dilatation and illumination. A method is proposed to address these extra challenges. The accuracy of the proposed algorithm was evaluated against corresponding measurement of eye torsion using the clips configuration measured on x-ray images. The algorithm developed in this study aims at estimating eye torsion by measuring the rotation of the iris pattern from a reference image to other images acquired during the course of the treatment. The basic steps to carry out the analysis are depicted in the diagram (figure) and can be summarized as follows:

- Iris Region Recognition And Intensity Correction
- Transformation To Polar Coordinates Of The Iris Region
- Distortion compensation by selection of region of interest (ROI)
- Computation of torsion by cross correlation of ROIs of reference and test image.

The intensity correction aims to correct uniformity of the light distribution on the images, and to enhance the iris structures in the ciliary region of the iris. It includes in sequence: noise removal, image sharpening and histogram equalization.

The presence of the cornea in front of the iris creates a distortion of the iris image proportional to the deviation of the optical axis from the resting position of the eye. For this purpose, a simplified model of the optical system was built using dedicated software (Zemax EE, Zemax Development Corporation, Washington, USA). It was identified that corneal distortion and perspective error are both minimized in the region laying over the axis defined by the azimuthal gaze direction and therefore these regions were used for computation of the shift of the iris pattern in the treatment image with respect to the reference image through normalized bi-dimensional cross correlation.

Concurrently to the acquisition of BEV images, a pair of orthogonal x-ray images of the patient clips was acquired. By rigid point-based registration, optimized in a least-square sense, one can align the Eyeplan eye model created during treatment planning to the clips' configuration captured at time of x-ray imaging. By rotational decomposition it is then possible to estimate the torsional component of the eye movement occurring between the reference image and other image acquisitions on a patient specific basis. This value of torsion is considered as the ground truth of torsional eye movement measurement as it originates from quantitative measurement of clips, surrogates rigidly attached to the patient's eye. The clip-based torsion is used to benchmark the iris-based torsion estimation algorithm and quantify its accuracy on the entire dataset of 20 patients included in this study.

On 20% of the overall number of instances however, the iris-based estimation of torsion was hindered by the inability of selecting a convenient ROI in the iris region due to eyelid occlusion or undesired light reflection. Thus, the iris-based algorithm is able to provide an estimate of torsional eye movements for 80% of the considered instances.

The iris-based torsion detection algorithm was compared to torsion deduced from x-ray images of the clips. A good and positive linear association was measured (R^2=0.71). The agreement between iris-based and clips-based estimation of torsion is between ± 1.5° for 85% of the cases, with 9% exhibiting discrepancies higher than 2°.

This study was supported by Personalized Health and Related Technologies (grant PHRT-524) and Swiss Cancer Research Foundation (grant KFS-4447-02-2018). Both grants are led by Dr. Jan Hrbacek at PSI. This study was recently published (Spaccapaniccia et al).

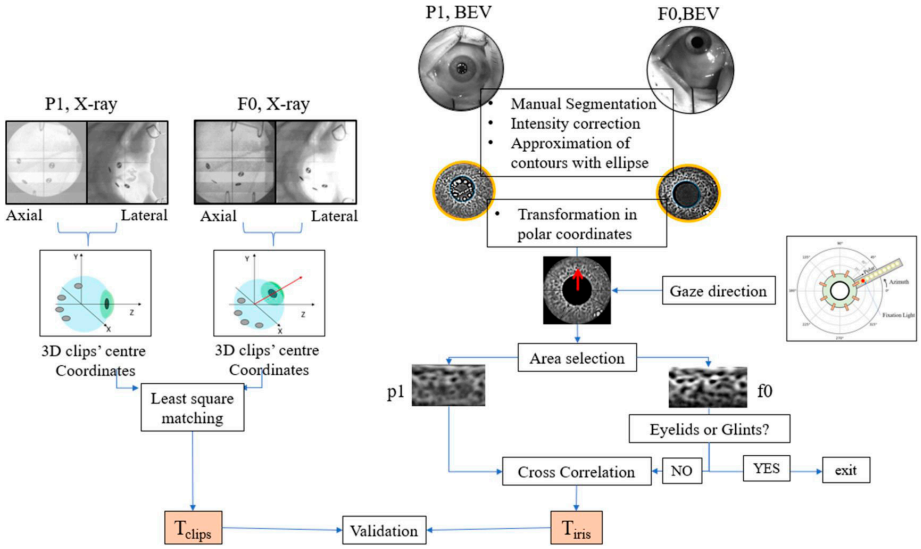


Figure: Methodology used in the present study. The x-rays images are used to compute the position in space of the eye and the torsion occurring between the two positions, while information on the rotation of the iris patter is extracted from the BEV images provided that the orientation of the eye in space is known.

Radio-Oncology News

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

Background and purpose

Sacral chordomas are locally aggressive and radio-resistant tumors. Proton therapy (PT) has the potential to deliver high radiation doses.The high radiation conformity and the reduction of the integral dose by the use of protons has made PT the standard radiation modality for the management of these tumors with increased tumor control and reduced toxicity rates. We assessed tumor control and radiation-induced toxicity retrospectively in a cohort of sacral chordoma patients treated at PSI with definitive or postoperative pencil beam scanning (PBS) PT.

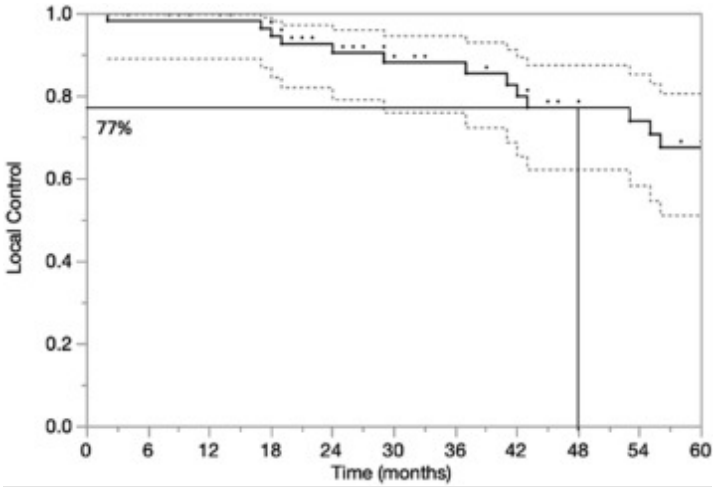


Figure: Local control in sacral chordoma patients (n=60)

Methods and Materials

Sixty patients with histologically proven sacral chordomawere treated between November 1997 and October 2018 with PBS PT at the Paul Scherrer Institute. Ten (17%) patients received combined photon radiotherapy and PT. Fifty (83%) patients underwent surgery and 10 (17%) had a biopsy only. For those undergoing resection, 33 (66%) underwent gross total resection. Patients received definitive or adjuvant RT to total doses ranging from 60.0 to 77.0 Gy(RBE) (median, 74) with single fraction doses from 1.8 to 3.0 Gy(RBE) (median, 2). During the median overall treatment time of 49 days (range 41–67), all patients received the total dose prescribed.Five (8%) patients with large inoperable tumours received additional concomitant hyperthermia up to 6 weekly sessions.

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 (CTCAE) v5.0.

Results

Median follow-up was 48 months (range, 4-186). Local recurrence occurred in 20 (33%) patients. Eight of these patients additionally showed distant failure before, after or with local failure. Distant failure only were observed in 2 patients. The 4 year-LC, FFDR, and OS rates were 77%, 89%, and 85%, respectively.

On univariate analysis, a significantly improved rate of local control was associated with gross total resection (p=0.02; hazard ratio (HR) 0.33, 95% confidence interval (CI) 0.13–0.85), no tumour extension beyond the bone (p=0.01; HR 0.11, 95% CI 0.01–0.85) and gross tumor volume smaller than 130 ml (p=0.4; HR 2.59, 95% CI 0.99–6.77).

On multivariate analysis, tumor extension restricted to bone (p=0.004), and gross total resection (p=0.02) remained independent favorable prognostic factors for local recurrence. No significant factors were identified for FFDR and OS.A trend towards statistical significance for OS was observed for gross total resection versus subtotal resection or biopsy (p=0.052),tumour restricted to bone (p=0.052) and GTV smaller than 130 ml (p=0.07). Of note, there was a suggestion of better local control with hypofractionation, although this did not reach statistical significance (p=0.07).

Twenty-four (40%), 28 (47%) and 8 (11%) patients experienced acute Grade (G) 1, G 2, and G 3 toxicities, respectively. Late grade 3 toxicity was observed in three (5%) patients. The 4-year late toxicity-free survival was 91% (95% CI 79-97). Two patients developed secondary malignancies to the bladder 3-7 years after PT.

Conclusions

The results of this retrospective analysis of patients with resectable and non-resectable sacral chordomas treated with high dose PBS PT is encouraging, with good tumour control rate and a low probability of late high-grade radiation-induced toxicity in most chordoma patients. Both the gross total resection and the tumour restricted to the bone were independent predictors of local tumour control.

This work has been recently published (Walser et al. 2021)

Imprint

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