Paul Scherrer Institut
Center for Proton Therapy
Newsletter #32_08/2024

Dear Reader

Welcome to this second 2024 edition of our SpotON+ Newsletter. In this edition, we report a small cohort of adolescents and young adults (AYAs or TYAs) (median age, 21.6 years) with sarcoma in the head and neck region. Most (57%) patients presented with rhabdomyosarcoma or Ewing sarcoma. Pencil beam scanning proton therapy was administered to a dose of 45 – 74 (median, 63) GyRBE, half of them with concomitant chemotherapy. With a median follow-up time of 57 months, five in field treatment failures were observed. Importantly, the estimated 5-year freedom from non-ocular high-grade toxicity was approximately 90%. Although a small cohort of AYAs, our data suggest excellent outcomes and these patients could benefit from protons in the light of the recent phase III US photon/proton trial in the H&N region.

The second paper reports the analysis of acute financial toxicity (FT) for 146 cancer patients living in Switzerland and undergoing proton therapy. Two countries are outliers when assessing the amount of money paid annually for health care, namely the US and Switzerland. For the former country, a recent survey has shown that the financial ill-being of cancer patients is substantial, with approximately 50% of them being in-debt after therapy and a further 13% expecting to be into debt soon at the time of this survey. Interestingly, 98% of respondents who reported being in debt were insured. In our country, health insurance is compulsory and one would expect that very few cancer patients would present with substantial financial toxicity in our small and high-income

country. Our analysis showed however, that a substantial number of them did present with acute FT during proton therapy, as assessed by the COST score that was a median 14 points under the perfect financial wellbeing threshold. A number of patients had various coping strategies, not limited but including using their savings (64%), spending less on leisure activities (37%) and even borrowing money (9.6%). These data shed an uncomfortable light on cancer management in Switzerland, FT being very mentioned, as in the US, to health care professionals. Dr. Bachtiary must be commended for conducting this prospective analysis in the time of the pandemic, which may have influenced somewhat the results. A follow-up study is on the drawing board and we plan to evaluate the non-acute FT of these patients this fall.

Finally, a paper assessing the uncertainties of deformable image registration (DIR) for dose accumulation assessment in proton therapy, delivered with a SIB paradigm, for head and neck cancer is summarized in this newsletter. In high dose gradients, substantial dose differences were observed when applying multiple DIRs. For the patient with the largest anatomical changes, the maximum uncertainty in the contralateral parotid was 33%. These data emphasize the necessity for quantifying deformable dose accumulation uncertainties in those patients treated with protons.

That being said, I hope this newsletter is of interest to you and I stay tuned for the next edition in about 4 month's time.

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

Radio-Oncology News

Pencil Beam Scanning Proton Therapy for Adolescents and Young Adults with Head and Neck Sarcomas

Purpose

Sarcomas are a rare group of tumors and more commonly develop in adolescents and young adults (AYAs). Head and neck sarcomas (HNSs) usually require a multimodal approach that includes chemotherapy, surgery, and/or radiation. Proton beam therapy has been shown to spare multiple organs at risk

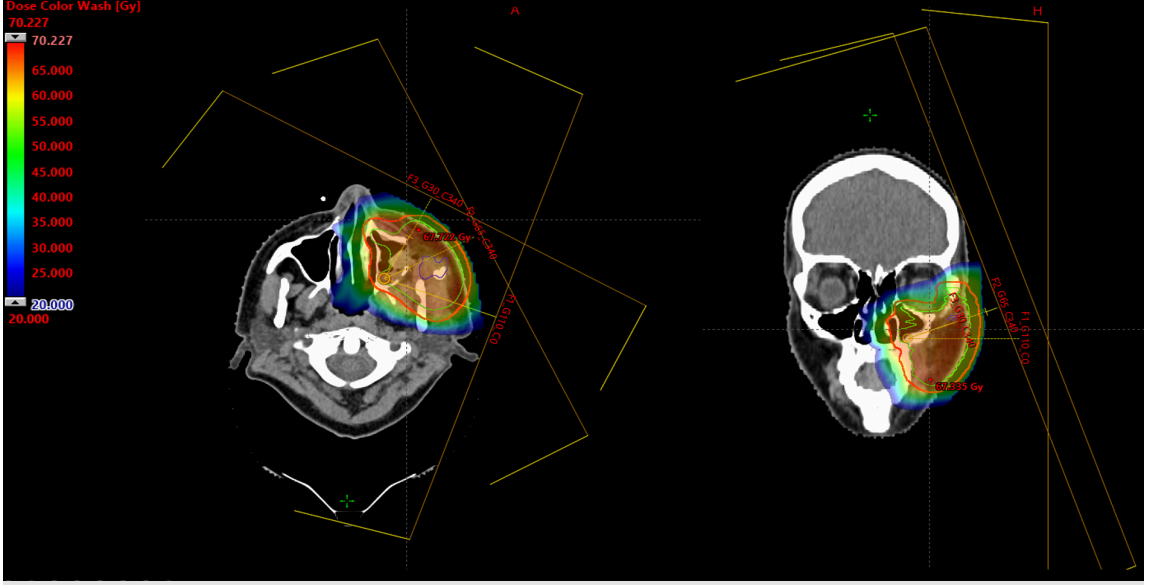
in head and neck tumors while maintaining or improving local control. The aim of this retrospective data analyses is to assess clinical outcomes of AYAs with HNSs treated with pencil beam scanning proton therapy (PBSPT) and to report quality of life.

Materials and Methods

Twenty-eight AYAs (aged 15 to 39 years) with HNSs treated between January 2001 and July 2022 at our institution were included. The median age was 21.6 years. Rhabdomyosarcoma (39.3%), Ewing sarcoma (17.9%), chondrosarcoma (14.3%), and osteosarcoma (14.3%) were the most frequent diagnoses. Three (10.7%) patients were metastatic before PBSPT and 13 (46.4%) patients had a tumor with intracranial extension. The median total radiation dose was 63 GyRBE (range, 45 to 74 GyRBE). Thirteen (46.4%) patients received concomitant chemotherapy. Toxicity was reported according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (US National Institutes of Health, Bethesda, Maryland). Survival was estimated using the Kaplan-Meier method. QoL was assessed using the validated PEDQOL (Pediatric Quality of Life Questionnaire) questionnaire. Self-reported outcomes were assessed using institutional questionnaires.

Results

With a median follow-up of 57 months (range, 3.7 to 243 months), 5 patients (17.8%) had local failure (LF) only, all of them were in-field. Two Patients (7.1%) experienced distant failure (DF) only, and 2 (7.1%) had LF and DF. The estimated 5-year local control (LC) and distant control (DC) rates were 71.8% and 80.5%, respectively. The median times to LF and DF were 13.4 and 22.2 months, respectively. Four (14.3%) patients died, all but one from their HNS. One patient developed metastatic breast cancer and died due to the disease. Estimated 5-year overall survival was 90.7%. All patients experienced acute toxicity, 22 of them had grade 2 or higher. Six (21.4%) patients developed nonocular grade ≥3 late toxicity, which consisted of otitis media (n = 2), hearing impairment (n = 2), osteoradionecrosis (n = 1), and sinusitis (n = 1). Four (14.3%) patients developed cataracts that required surgery. The 5-year freedom from nonocular grade 3 toxicity was 91.1%. No grade 4 or higher toxicity was observed. Adolescents rated their quality of life before treatment worse than their parents did. The most pronounced difference in scores emerged in the domains of autonomy and cognition, while the differences between adolescents and parents were smaller for physical functioning and social interactions within the family.



Proton therapy plan dose distribution and beam arrangement of an 18 years-old teenager with an osteosarcoma of zygomatic bone.

Conclusion

Excellent outcomes with acceptable late-toxicity rates were observed for AYAs with HNS after PBSPT.

This work has been recently published (Vazquez et al. 2023).

Radio-Oncology News

Financial Toxicity in Swiss Cancer Patients with Proton Therapy: An Observational Cross-Sectional Study on Self-Reported Outcome

Background

Proton therapy is indicated for cancers that would be difficult to treat with conventional radiotherapy. Compulsory healthcare insurance covers the costs of this therapy in Switzerland, but this does not mean that proton therapy is cost-neutral for every cancer patient. Significant out-of-pocket (OOP) costs may arise due to expenses associated with proton therapy, and patients may experience treatment-related financial distress. This financial distress adversely affects patients' quality of life, treatment choice, treatment compliance, and treatment outcome. It can be just as toxic as other therapy modalities. Therefore, treatment-related financial distress has been defined as "financial toxicity." This study investigates the financial toxicity of patients undergoing proton therapy in a high-income country with a compulsory health insurance policy.

Methods

Between September 2019 and November 2021, 146 Swiss cancer patients treated with proton therapy participated in this study, of whom 90 (62%) were adults and 56 (38%) were caregivers of child cancer patients. OOP costs were recorded weekly during proton therapy. Financial toxicity was assessed using the validated self-reported FACIT Comprehensive Score for Financial Toxicity (COST). The overall score ranges from 0 to 44, with a lower score indicating low financial well-being. The COST score and the financial coping strategies were captured at the end of treatment. Multiple linear regression models were used to quantify the association between disease-specific and patient-specific parameters and COST outcomes.

Weekly recording of additional costs

Study to assess the Financial Burden of Cancer Patients receiving Proton Therapy

Week 1

Medical costs	Amount in Swiss Francs
Medication	
Stationary stay in hospital	
Ambulant medical consultations (e.g. eye specialist, ENT specialist)	
Ambulant therapy (e.g. chemotherapy, hyperthermia)	
Nursing aids (e.g. ointments, mouthwash, bandaging material, food supplements)	
Medical services (e.g. nutrition counselling, physical therapy)	
Other costs, if so, which:	

Week 1

Non-medical costs	Amount in Swiss Francs
Travel/drive to PSI and back	
Accommodation due to the treatment	
External meals due to the treatment	
Phone calls due to the treatment	
Household help due to the treatment (e.g. babysitter, cleaning person)	
Leisure activities due to the treatment (e.g. cinema, zoo)	
Other costs, if so, which:	

Extract from the Cost Diary (cover sheet and first week of treatment). This diary was handed over to the patients to record their out-of-pocket costs during proton treatment.

Findings

The median COST score, indicating financial toxicity, was 29.9 (IQR 21.0; 36.0) for all patients, 30.0 (IQR 21.3; 37.9) for adults, and 28.0 (IQR 20.5; 34.0) for children's caregivers. Higher income was significantly associated with higher COST scores, indicating less financial toxicity ($p \leq 0.001$). Further distance from home to the treatment centre per 100 km was significantly associated with lower COST scores, indicating increased financial toxicity ($p \leq 0.001$). Married adult patients as well as adult patients living in a permanent partnership had substantially lower COST scores than single patients ($p \leq 0.008$). Age, gender, educational level or employment status showed no impact on the financial toxicity of adult patients. The median OOP cost was 2050 Swiss francs and was spent mainly on travel (median 800) and eating out (median 200). Sixty-three (43%) patients used their savings; 54 (37%) cut spending on leisure activities; 21 (14.4%) cut living expenses; 14 (9.6%) borrowed money; nine (6.2%) worked more; and four (2.7%) sold property. Patients with high COST scores used significantly fewer coping strategies such as saving on leisure activities ($p \leq 0.001$), spending savings ($p = 0.002$), borrowing money ($p = 0.003$), and increasing workload ($p = 0.035$).

Conclusions

A substantial number of cancer patients treated with proton therapy experience financial toxicity in Switzerland. Long travel distances to the proton therapy centre and low income negatively affect the financial well-being of these patients during proton therapy.

This work has been recently published (Bachtiary et al. 2023).

Medical-Physics News

Quantification of deformable image registration uncertainties for dose accumulation on head and neck cancer proton treatments

Background and Motivation

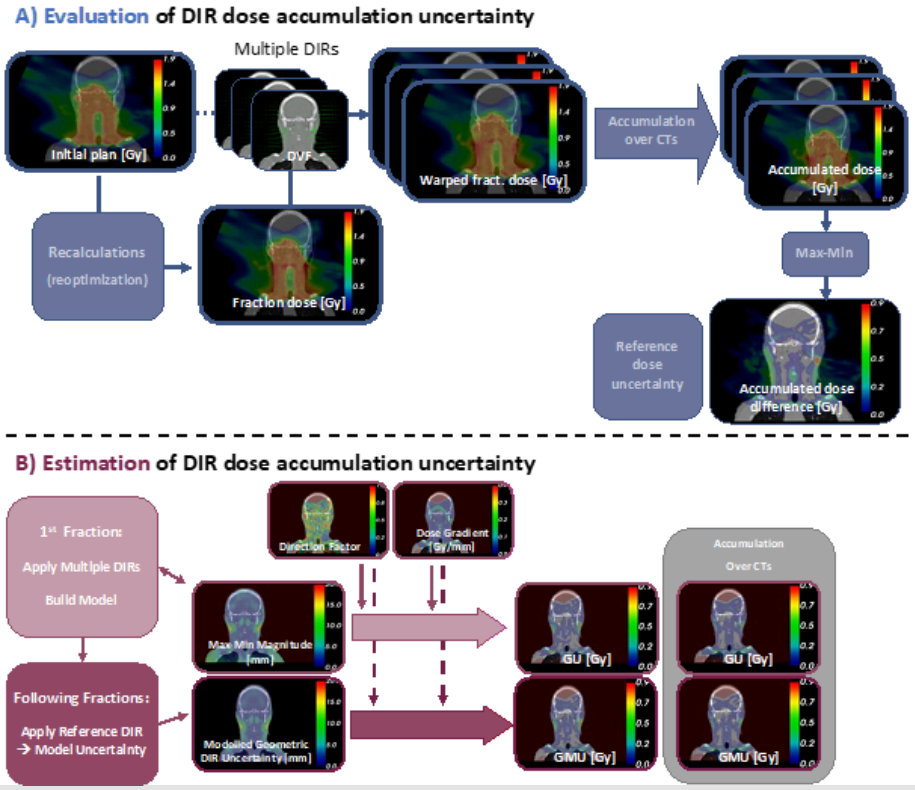
Adaptive radiotherapy is required for patients with substantial anatomical changes during therapy. Various opportunities and challenges are introduced with adaptive radiotherapy, such as dose accumulation over the course of the treatment to have a complete picture of the delivered dose. Deformable image registration (DIR) is used in this process, but it poses challenges due to its inherent uncertainties, which often hinder further clinical implementation up to now. This study investigates the importance of quantifying uncertainties in deformable dose accumulation (DDA) for head and neck cancer (HNC) patients undergoing proton therapy. The pathway to more quantitative DDA uncertainties investigated can be extended to other radiotherapy modalities.

Methodology and Approach

Five head and neck cancer (HNC) patients with multiple CT scans taken during treatment were retrospectively investigated. A simultaneous-integrated boost (SIB) proton plan was optimized. The doses were recalculated on the repeated CTs and warped using multiple DIRs from repeated to reference CTs. The dose ranges were determined on a voxel-by-voxel level to provide error bars for DDA. An early-stage DDA uncertainty estimation method without applying multiple DIRs for each fraction, previously tested for lung cancer, was applied to HNC. This method combines geometric DIR uncertainties, dose gradients, and their directional dependence.

Results

Significant dose differences were observed when applying multiple DIRs, especially in high dose gradient regions. For the patient with the largest anatomical changes (−13.1% in body volume in the region of interest), the maximum uncertainty in the contralateral parotid was 33%, with 54% of voxels presenting an uncertainty >5%. Accumulating doses over multiple CTs partially mitigated these uncertainties. The estimation approach predicted 92.6% of voxels within ±5% of the reference dose uncertainty across all patients.



A) Dosimetric DIR uncertainty evaluation by applying multiple DIRs for each fraction. B) Uncertainty estimation approach using a geometric DIR uncertainty, the dose gradient and a direction dependence.

Conclusions

DIR variations significantly impact accumulated doses, emphasizing the need for quantifying DDA uncertainties in HNC patients. Multiple DIRs help quantify these uncertainties, particularly for patients with large anatomical changes and

in dose gradient regions. The estimation approach previously proposed for lung cancer, was successfully validated, showing that it works well for HNC and SIB plans, which present different dose gradients.

This research highlights the following key points for adaptive HNC radiotherapy:

1. **DDA Uncertainty Awareness:** Understanding DDA uncertainties is crucial, especially in patients exhibiting substantial anatomical changes.
2. **Multiple DIRs for Quantification:** Employing multiple DIRs aids in quantifying DDA uncertainties.
3. **Uncertainty Estimation:** Using dose gradients in combination with geometrical DIR uncertainties offers a practical tool for assessing DDA uncertainties for HNC cases.

This work contributes to ongoing efforts in quantifying DDA uncertainties, promoting informed decision-making, and potentially leading to the development of DDA uncertainty tolerance levels in adaptive radiotherapy.

This work has been recently published (Amstutz et al. 2024)

Imprint

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