Physics and Imaging in Radiation Oncology 21 (2022) 134–135

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Editorial

# Towards an integral clinical proton dose prediction uncertainty by considering delineation variation

Proton therapy is more susceptible to uncertainties of the beam placement compared to conventional radiotherapy due to the finite range of protons in the patient. To ensure target coverage, additional healthy tissue around the target volume is irradiated in clinical routine. Advancements in both patient imaging and treatment planning therefore aim to reduce these clinical safety margins. However, any reduction of the overall safety margin also reduces the possibility to compensate for uncertainty sources that are not explicitly considered in the uncertainty estimation and therefore comes with a risk of decreased target coverage [1]. At the same time, an appropriate technique for combining and considering the different uncertainties in the treatment planning process is necessary as not to dilute technical advancements.

Uncertainties in proton therapy planning and delivery originate from the whole treatment chain, starting from patient imaging and the subsequent target and organ-at-risk delineation, across to treatment planning, patient positioning and finally beam delivery, with each uncertainty factor in itself describing a combination of different uncertainties [2]. Several approaches to combine errors in radiotherapy have been investigated, such as the straightforward calculation of (weighted) sums where assumptions regarding the error distribution are implicitly included [2,3], or more complex approaches such as numerical error sampling, relying on probability density functions (PDFs) [4,5]. A comprehensive framework for combining *Type A* uncertainties (those obtained as standard deviation from repeated measurements) and *Type B* uncertainties (those based on scientific judgement by assigning PDFs) is given in the *Guide to the expression of Uncertainty in Measurement* [6], which has also been applied for uncertainty estimation in proton therapy [7,8]. Resulting uncertainty factors regarding patient setup, range prediction and organ motion can furthermore be considered in treatment planning by examining dose distributions for different error scenarios [9–12].

A major uncertainty factor, considered only implicitly as part of the safety margin, is the target delineation. It depends not only on the available image information, which is ambiguous due to microscopical anatomical spread not being visible – typically considered by increasing the gross tumor volume by several millimeters, depending on the tumor site – but also on the level of training received by the clinician performing the delineation (the 'observer'), leading to large inter-observer variation (IOV) depending on the skill level. With the risk of treatment-center-specific systematic deviations, e.g. due to different interpretation of clinical guidelines, this potentially makes delineation the *weakest link* in accurate proton treatment planning. This can only be intercepted by (large) safety margins [13].

However, no consensus on the necessary level of uncertainty exists yet. While numerous studies were performed, they lack methodological consistency, making it difficult to pin down an uncertainty to cover both the accuracy and variation in delineation [14]. There is only limited data on the resulting variation in target expansion between treatment centers. While for prostate cancer- and brain tumor patients the variation is on the level of or exceeding patient setup-up errors [15], the target expansion varies greatly in the heterogeneous head and neck region, ranging from 0 to 15 mm between treatment centers [16].

The presented work by *Hofmaier* et al. [17], published in this virtual special issue of physics highlight papers from the recent ESTRO 2021 conference, quantitatively assesses the impact on calculated dose of IOV in target delineation in combination with uncertainties in patient setup and range prediction. The work utilizes a Monte-Carlo variance-based sensitivity analysis framework [18] for error combination, where input parameters are sampled from assumed uncertainty distributions as well as from a set of delineations to quantify their influence on dose calculation and consequently dose/volume parameters. The approach allows for a direct, patient-specific quantification of the individual uncertainty factors, which can be used to support decision making in the clinical plan evaluation process. For individual patients in a small cohort of benign skull base meningioma patients, the authors traced back relevant deteriorations on $D_{95\%}$ of the clinical target volume to the variations in delineation.

It should be noted that their specific metric for the IOV was calculated from different target volume delineations and a consensus target volume obtained with the STAPLE algorithm [19]. This makes the presented results susceptible to individual delineations deviating from the group, as also pointed out by the authors. A different metric choice may lead to completely different results. The presented work is therefore first of all a feasibility study on how delineation uncertainties in proton therapy can be considered on a patient-individual level as part of a sensitivity analysis. At the same time, a major benefit of the framework is its adaptability in including different uncertainty sources, such as relative biological effectiveness, as done in previous publications from the authors [20], with the major limiting factor being computation time.

A future application of the presented framework on a larger patient cohort of primary brain tumor- as well as pelvic cancer patients may allow for a better understanding of the degree to which current clinical safety margins cover variations in delineation. There, an IOV metric more robust against outliers is needed. In clinical routine, where the labor-intensive delineation by multiple clinicians is generally unfeasible, the application of the framework on contours from different automated delineation approaches may prove beneficial to identify patients either requiring larger or allowing for smaller safety margins.

https://doi.org/10.1016/j.phro.2022.03.001

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: OncoRay has an institutional research agreement with Siemens Healthineers in the field of dual-energy CT for particle therapy (2016–2020). Furthermore, OncoRay has an institutional agreement as reference center for dual-energy CT in radiotherapy as well as a software evaluation contract with Siemens Healthineers.

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