Physics and Imaging in Radiation Oncology 29 (2024) 100560

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

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

Editorial

The role of 4D particle therapy in daily patient care and research

Current radiotherapy planning and delivery technologies allow for the treatment of most relevant tumour sites with excellent precision. Advanced imaging options, adaptive treatment concepts and the possibility to choose out of a toolbox of a variety of treatment techniques are opening a new era of radiation oncology. Due to its favoured depth dose characteristics and sharp lateral penumbra particle therapy has a high potential to spare organs at risk adjacent to the tumour region while escalating dose if necessary. However, in the presence of interfractional anatomical changes and intrafractional tumour and organ motion, the pronounced range sensitivity of protons and carbon ions poses further challenges. To treat moving targets with charged particles motion management strategies need to compensate for additional uncertainties compared to photon therapy, such as the interplay between spot delivery patterns and tumour motion.

To collect recent research strategies and findings in the field of “4D particle therapy” a topical virtual special issue (VSI) was compiled in Physics and Imaging in Radiation Oncology (*phiRO*) in connection with the *4D Treatment Workshop for Particle Therapy* [1–10]. Together with technical innovations for (4D) imaging, dose calculation and robust optimisation harmonisation of treatment schemes have shown to be highly relevant for the success of clinical implementation of 4D mitigation methods. This trend was reflected both in surveys on practice patterns related to inter- and intrafractional motion management as well as in reports on clinical practice [1,2,8,10–12]. This knowledge and experience is adding to other adaptation-focused papers in our journal addressing comparable challenges in photon or proton-based radiotherapy (e.g. [13–17]).

Robust optimisation and 4D dose calculation is one of the current topics dominated by the particle therapy community, yet also highly relevant for photon-based radiotherapy. Spautz et al [3] explored the impact of inter- and intrafractional variations reflecting the current trend adressing temporal changes in a comprehensive way. They considered motion-induced changes based on breathing and machine log files as well as anatomical changes together with setup and range uncertainties. Taking into account planning computed tomography (CT), amplitude-based 4D-CT and control CT images, the potential of five different robust optimisation methods (based on average CTs and 4D-CT phases) was investigated using retrospective 4D dose calculation. Without rescanning none of the robust optimisation methods provided sufficient target coverage in the presence of intrafractional target movements larger than 10 mm. Setup and range uncertainties were well compensated, while interfractional changes caused a loss in target coverage for all treatment plans. One remarkable result was that the optimisation on three 4D-CT phases was sufficient and could considerably reduce the computational time. While retrospective machine log file based 4D dose calculation was investigated by several groups in the past (e.g. [18–20]) prospective 4D dose prediction has the potential to react on the motion sensitivity of a treatment plan. The contribution by Lebbink et al [4] showed that for liver and lung patients with small motion amplitudes, a simple 4D dose calculation can identify outliers and reliably predict the intrafractional dose distortion. Additionally, phantom measurements confirmed these results for large motion amplitudes. The use of constant accelerator delivery and individual breathing parameters extracted from the 4D-CT for prospective 4D dose prediction is an important step towards realising efficient and continuous motion surveillance before and during treatment.

The need for implementing 4D dose calculation including uncertainty evaluation into clinical software tools was also one of the top requirements identified in the survey by Zhang et al [2] on practice patterns for real-time intrafractional motion management in particle therapy. Most of the included particle therapy centres used active motion management strategies in their clinic with deep-inspiration breath hold techniques being most frequently used. Technical limitations and limited resources were identified as the main barriers to implementing more complex solutions. The second survey on adaptive particle therapy in this VSI underlined the increasing relevance of catching up with online adaptive solutions available for photon-based radiotherapy [1,10–12]. Missing technological developments from the industrial side as well as insufficient levels of automation hinder the implementation of online adaptation strategies, while better 4D image quality is needed for real-time motion assessment and prediction.

Time-resolved imaging is the basis for identifying tumour and organ motion patterns on an individual basis. At the treatment planning stage, high geometrical accuracy of respiratory 4D-CT and magnetic resonance (MR) imaging are essential [21], while online adaptation and tumour tracking rely on high-speed 4D image acquisition and reconstruction [5]. In that context, Schmitz et al [6] demonstrated that 4D cone beam CTs with suitable intensity correction can support the assessment of daily variations in tumour motion and its effect on the dose calculation. Time-resolved volumetric MR provides anatomical images with high temporal resolution for motion modelling. This increased accuracy is of particular interest for particle therapy to predict the interference between beam delivery, tumour and organ motion. For that purpose, Peteani et al [7] modelled anatomical changes in lung cancer patients occurring over several minutes by retrospectively reconstructing 4D-MR images from interleaved cine sequences. By that, they aimed to overcome the drawback of 4D-CTs providing only information for one averaged cycle potentially influencing delivery accuracy.

Many of the described aspects were put in perspective to the existing literature in the topical review article on the clinical introduction of 4D

https://doi.org/10.1016/j.phro.2024.100560

Available online 19 February 2024

particle therapy [8]. In addition to the comprehensive overview of the literature, this review article summarised exemplary workflows for treating moving targets as implemented at selected particle therapy centres. 4D optimisation and calculation methods could be identified as a common and favoured approach to mitigate and evaluate motion. This again underlined that regular control imaging and 4D dose prediction are crucial to ensure the required precision in adaptive treatment schemes throughout the whole treatment course. Important findings and future directions for advancing the field of 4D and adaptive particle therapy were collected in original, survey and review papers from leading groups in this *phiRO* VSI, supporting promising implementations and cooperations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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