Log file based dose reconstruction and accumulation for 4D adaptive pencil beam scanned proton therapy in a clinical treatment planning system: Implementation and proof-of-concept

Meijers, A.; Jakobi, A.; Stützer, K.; Marmitt, G.; Both, S.; Langendijk, J.; Richter, C.; Knopf, A.;

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Log file based dose reconstruction and accumulation for 4D adaptive pencil beam scanned proton therapy in a clinical treatment planning system: Implementation and proof-of-concept

A. Meijers[1], A. Jakobi[2,3,4], K. Stützer[2,4], Gabriel G. Marmitt[1], S.Both[1], J.Langendijk[1], C. Richter[2,3,4,5,*], A. Knopf[1,*]

[1]University of Groningen, University Medical Center Groningen, Department of Radiation Oncology, Groningen, The Netherlands
[2]OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden - Rossendorf, Dresden, Germany
[3]Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[4]Helmholtz-Zentrum Dresden - Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany
[5]German Cancer Consortium (DKTK), partner site Dresden, and German Cancer Research Center (DKFZ), Heidelberg, Germany
* shared last authorship

Corresponding author: Antje Knopf, UMCG - Hanzeplein 1, 9713 GZ Groningen, Netherlands, E-mail: A.C.Knopf@umcg.nl

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Abstract

Background and Purpose

Motion induced uncertainties hamper the clinical implementation of pencil beam scanning proton therapy (PBS-PT). Prospective pre-treatment evaluations only provide multi-scenario predictions without giving a clear conclusion for the actual treatment. Therefore, in this proof-of-concept study we present a methodology for a fraction-wise retrospective 4D dose reconstruction and accumulation aiming at the evaluation of treatment quality during and after treatment.

Material and Methods

We implemented an easy-to-use, script-based 4D dose assessment of PBS-PT for patients with moving tumours in a commercially available treatment planning system. This 4D dose accumulation uses treatment delivery log files and breathing pattern records of each fraction as well as weekly repeated 4D-CT scans acquired during the treatment course. The approach was validated experimentally and was executed for an exemplary data set of a lung cancer patient.

Results

The script-based 4D dose reconstruction and accumulation was implemented successfully, requiring minimal user input and a reasonable processing time (around 10 minutes for a fraction dose assessment). An experimental validation using a dynamic CIRS thorax phantom confirmed the precision of the 4D dose reconstruction methodology. In a proof-of-concept study, the accumulation of 33 reconstructed fraction showed a linear increase of D98 values. Projected treatment course D98 values revealed a CTV under dosage after fraction 25. This loss of target coverage was confirmed in a DVH comparison of the nominal, the projected (after 16 fractions) and the accumulated (after 33 fractions) dose distribution.

Conclusions

The presented method allows for the assessment of the conformity between planned and delivered dose as the treatment course progresses. The implemented approach considers the influence of changing patient anatomy and variations in the breathing pattern. This facilitates treatment quality evaluation and supports decisions regarding plan adaptation. In a next step, this approach will be applied to a larger patient cohort to investigate its capability as 4D quality control and decision support tool for treatment adaptation.

Introduction

Treatment of moving tumours in the lung with pencil beam scanning (PBS) proton therapy has been identified as being challenging early on [1]. This has mainly two causes: First, large density changes in the treated area. A tumour movement out of the planned treatment position largely impacts the range of the proton beam. Second, motion of the tumour takes place at the same time scale as the motion of the pencil beam during treatment, causing the so-called interplay effect by beam and motion interference. This effect can lead to highly inhomogeneous dose distributions and was, up to now, substantially explored in phantom measurements and treatment planning studies [2–6]. These studies identified a multitude of influencing factors, e.g. patient-specific parameters like motion amplitude and tumour position at treatment start as well as machine-specific parameters like pencil beam spot size and the time required for spot repositioning. Most evaluations agree that the impact of the interplay effect is highly individual for a specific set of patient characteristics and machine parameters as well as their specific combinations per treatment fraction. Thus, it is hard to predict the dosimetric consequences of the tumour motion in advance in a pre-treatment evaluation. Such prospective pre-treatment evaluations consist of multiple scenarios, based on nominal patient and treatment machine characteristics. These analyses are clinically relevant as they aim on assessing before treatment whether the worst possible dose distributions would still be acceptable for treatment. Nevertheless, by taking such an approach, the treatment plan may be optimized to be robust against scenarios that might never occur during the actual treatment. Therefore, the actual dose degradation per fraction, which remains unknown in the multi-scenario approach, is also of great importance in the clinical assessment of the treatment quality and has been identified by the community as an “essential [need] for a comprehensive and safe clinical implementation of scanned particle treatment for

moving targets” [7]. Subsequently accumulated dose distributions during the course of treatment can be used to support decisions on the treatment adequacy and the need of treatment adaptation. Furthermore, a realistic accumulated dose distribution for the full treatment course is a better basis for correlations with side effects and recurrences. The actual fraction dose distribution of PBS treatments can be evaluated retrospectively by using the required information from the treatment machine, i.e. at which time point precisely which spot was applied at which geometric position, and from the patient, i.e. in which position the patient anatomy was at the time of a particular spot delivery. Richter et al. [8] presented such an approach for liver treatment with carbon ions using an in-house developed software.

An experimental validation of an in-house deforming grid 4D dose calculation implementation for PBS proton therapy was recently presented by Krieger et al. [9]. A single-field plan was delivered to a homogeneous PMMA phantom and measured by a high-resolution scintillating-CCD system. Various motion scenarios were simulated using a 4D Quasar phantom and logged by an optical tracking system in real-time. It was shown that the deforming grid 4D dose calculation was able to predict the complex patterns of 4D dose distributions with high dosimetric and geometric accuracy. In a paper by Kimpki et al [10] the utility of this in-house deforming grid 4D dose calculation for the evaluation of different pencil beam scanning techniques in terms of effectiveness and efficiency of rescanning moving targets was demonstrated. A 4D dose calculation routine for PBS proton therapy using machine log files and motion pattern was also recently implemented in RayStation by Pfeiler et al. [11]. In a simple phantom setup it was shown that this implementation could be used to evaluate interplay effects. Our work extends these 4D dose calculation implementations by also allowing for a subsequent dose accumulation and applying it to a complex clinical use case.

In this paper, we describe a proof-of-concept study investigating the feasibility of fraction-wise retrospective dose reconstruction and subsequent dose accumulation in a commercial treatment planning system using its scripting functionality. For most realistic dose assessment, input data comprised the treatment delivery machine log files of 33 fractions and the patient's breathing patterns, which were acquired during treatment, as well as weekly acquired 4D-CT datasets taken throughout the treatment course.

Materials and Methods

Patient data

The study was performed with imaging and respiratory motion data from a patient with a non-small cell lung cancer stadium IIIB (T1aN3M0) of an on-going prospective clinical trial (PRONTOX, ClinicalTrials.gov Identifier NCT02731001 [12]) at OncoRay (Dresden, Germany), who had given informed consent to the scientific use of his data. Clinical target volume (CTV) was defined with an 8 mm margin based on the internal gross tumour volume (iGTV) delineated on time-resolved computed tomography (4D-CT) images and the lymphnode GTV. Contoured organs at risk (OAR) comprised lungs, spinal cord, heart, brachial plexuses and oesophagus.

Imaging data

4D-CT imaging was performed with an in-room Siemens Somatom Definition AS (Siemens Healthineers, Germany) coupled to a pressure belt system (ANZAI, Japan) for motion surrogate retrieval. One pre-treatment 4D-CT and five weekly control 4D-CT datasets taken in treatment position at fractions 7, 13, 19, 25, and 31 were acquired, each comprising eight breathing phases and an average CT. The initial tumor motion (3D vector of the centroid position of the tumor) in

the planning 4D-CT was of 0.7mm, varying between 0.5mm, 0.8mm, 0.3mm, 0.4mm and 1mm in the repeated 4D-CTs of week 1, 2, 3, 4 and 5.

Motion output files were acquired during 22 out of 33 fractions delivered in free breathing, using the same ANZAI belt as during 4D-CT acquisition (Figure 1). For the remaining 11 out of 33 fractions motion monitoring was not possible due to practical reasons in the clinical workflow (e.g. delay in treatment schedule resulting in the decision to skip optional respiratory signal measurement).

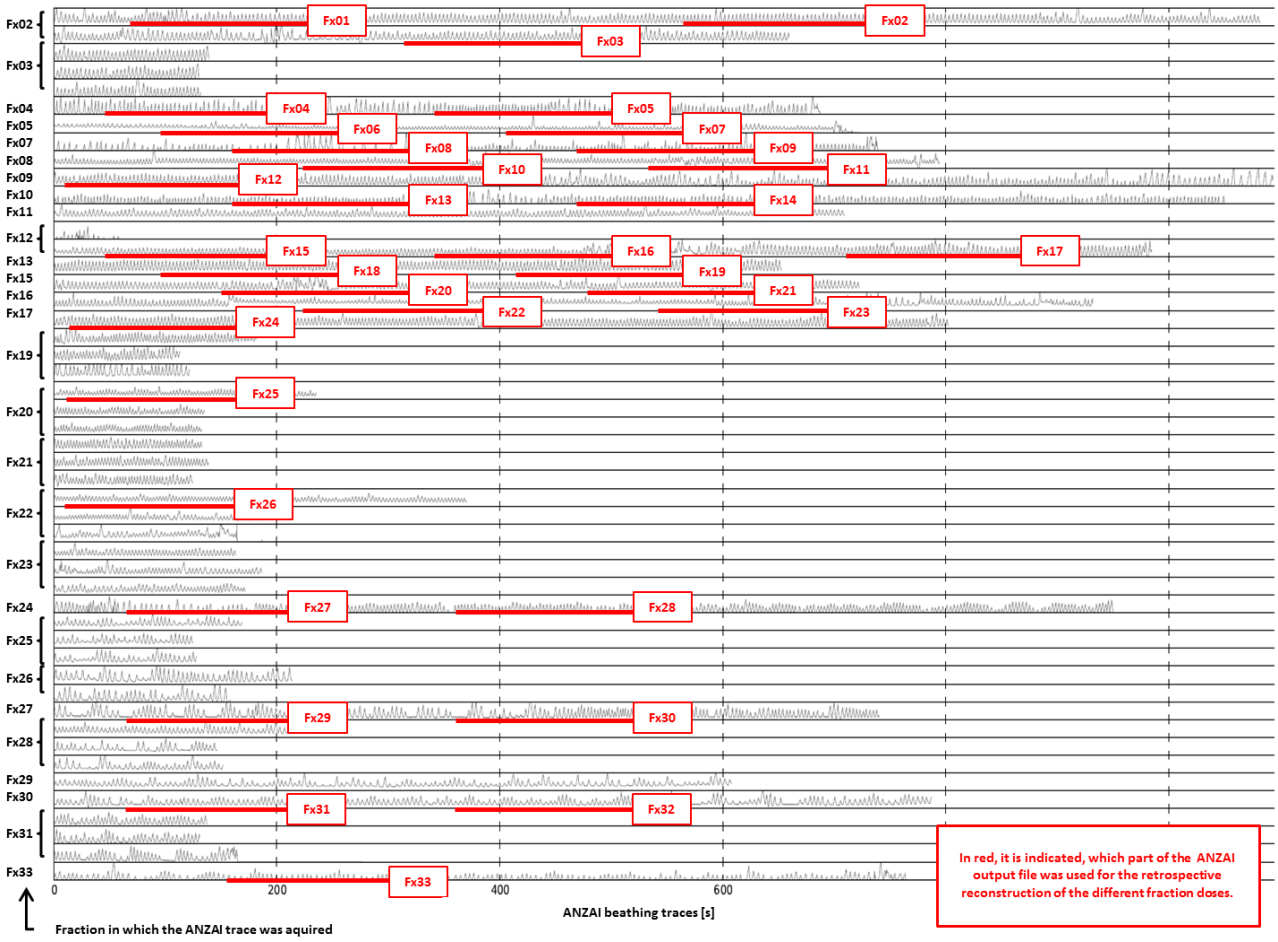

Figure 1: Overview of used motion monitoring data.

Image registration

Six degrees-of-freedom rigid registrations were performed between the planning 4D-CT and the sequential control 4D-CTs. The registrations focused on bony structures, especially the vertebral bodies close to the target, similar to the actual treatment setup. For voxel mapping, deformation vector fields were generated between the planning and control 4D-CTs using the built-in hybrid deformable image registration algorithm ANACONDA of the treatment planning system RayStation 6 (RaySearch, Sweden). ANACONDA combines image information, such as intensities, with anatomical information provided by contoured image sets and performed best in a recent assessment of dosimetric errors induced by various deformable image registration methods in 4D PBS proton treatment planning [13]. In our data set the lungs were used as controlling region of interest. The quality of the deformation vector fields was assessed by mapping and manually reviewing the structures from the reference image to the other CT image datasets as well as checking the vector fields visually for consistency and plausibility.

Treatment planning

PBS proton treatment planning was done with RayStation 6 using the CTV as target and the IGTV density assigned to muscle tissue. The PBS plan was designed with two beams (0°, 145°) and optimised aiming for robustness against 5 mm setup and 3.0% range uncertainty. Optimisation focused on adequate target coverage: V_{95}>98% of prescribed dose of 66 Gy(RBE) and minimisation of OAR dose. The Monte Carlo dose calculation engine was used to calculate the final dose. Dose evaluations were based on perturbed dose and were acceptable with nominal plan values for CTV V_{95}=97.4%, spinal cord D_1=29.5 Gy(RBE), heart D_{mean}=2.7 Gy(RBE), lungs D_{mean}=8.2 Gy(RBE) and oesophagus D_{mean}=17.6 Gy(RBE).

Simulation of PBS treatment – 4D calculation

33 machine log files of the PBS treatment were obtained from dry run deliveries at the clinical proton treatment facility at UMCG (Groningen, Netherlands) equipped with the IBA Proteus®PLUS system (IBA, Belgium).

Post-processing of the output files of the ANZAI motion monitoring system and the IBA machine delivery log files were performed with in-house scripts (Python), which can be executed directly in RayStation via the scripting module. Analysed log file data included spot energy, spot position on IEC x and y axis at iso-centre plane, delivered monitor units per spot and absolute time point of spot delivery.

For each fraction, the dose of each delivered spot was mapped to a 4D-CT phase by combining the log file and a selected part of an ANZAI output file. Figure 1 shows which part of the ANZAI output file was used for specific fraction. For this proof-of-concept, this selection was arbitrary just assuring that the selected part of an ANZAI output file covered the beam delivery duration. Spot delivery times were compared to the ANZAI output file, determining the breathing phase of the patient at spot delivery and assigning the spots to the corresponding 4D-CT phases. For each fraction, the most recent 4D-CT image dataset was used, as illustrated in Figure 2. With the available data, a set of eight sub-plans in DICOM format corresponding to the eight 4D-CT phases was created for each fraction. Each sub-plan contained only the spots that corresponded to the associated phase of the breathing cycle.

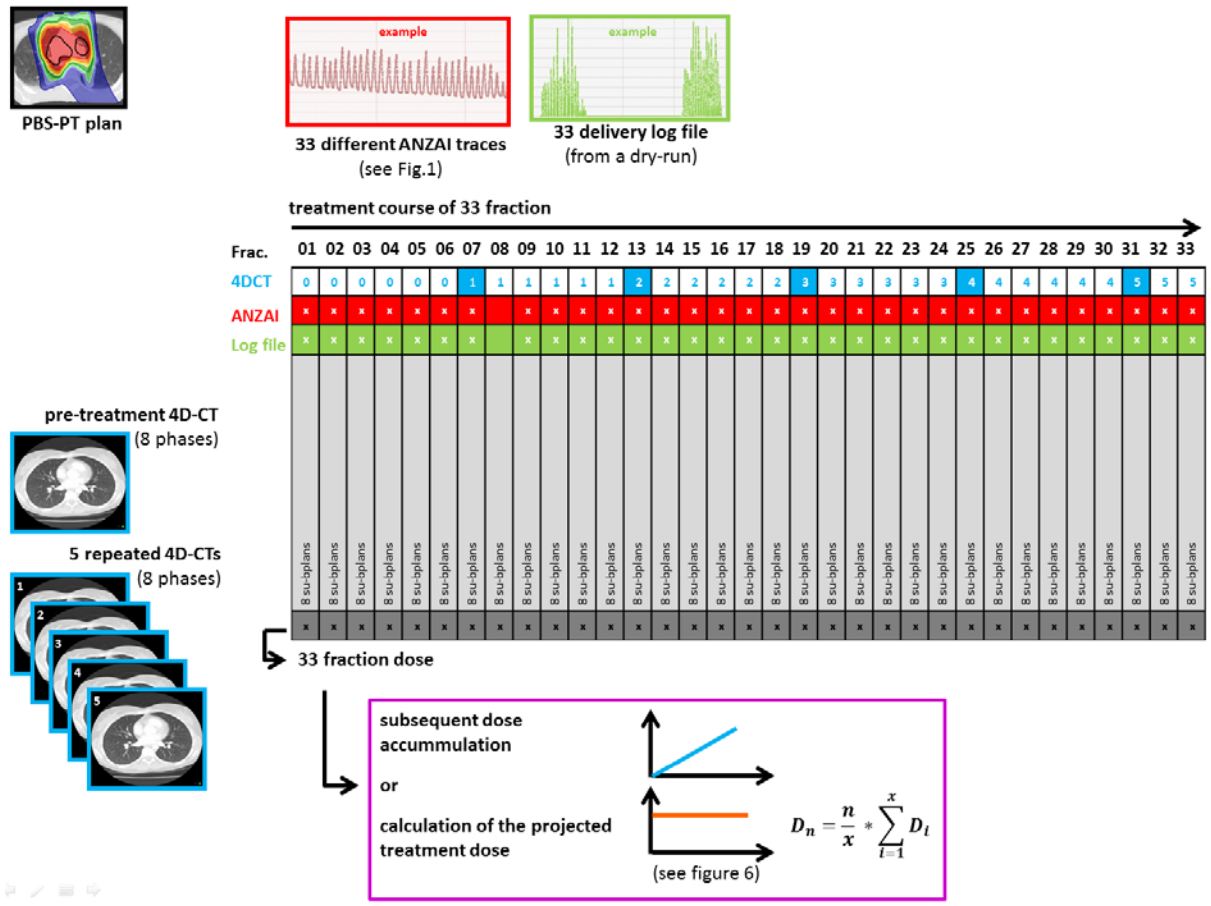

Figure 2: Overview of the data set used to demonstrate the workflow for fraction-wise retrospective 4D dose reconstruction for moving targets.

Those sub-plans were re-imported in RayStation and recalculated on the corresponding 4D-CTs. The dose distributions of the different respiration phases were warped using deformable image registration, and summed on the reference CT. This procedure resulted in one dose distribution per fraction taking into account weekly anatomical changes, daily varying organ motion, setup changes and the interplay effect. The accumulated treatment course dose was calculated at the end of the treatment by summing all fraction doses. Furthermore, projected full treatment course doses D_n after x of n fractions following formula [1] were calculated after each treatment fraction by summing the available fractions and scaling them to match the total course dose.

$$D_n = \frac{n}{x} \cdot \sum_{i=1}^{x} D_i \qquad [1]$$

The entire proposed clinical workflow is sketched in Figure 3.

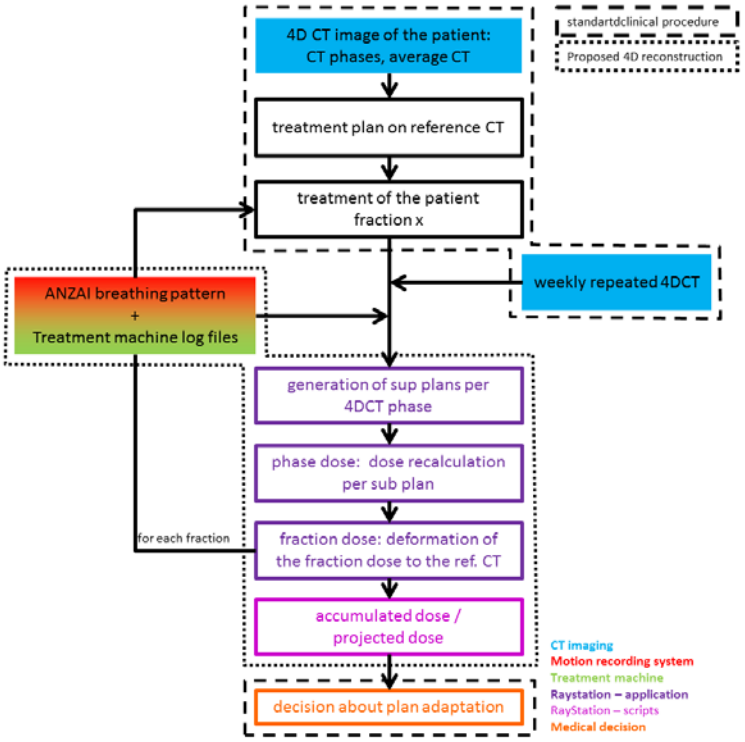

Figure 3: Implemented workflow for fraction-wise retrospective 4D dose reconstruction for moving targets supporting the medical decision in respect to treatment adaptations.

Experimental validation

To experimentally validate the 4D dose reconstruction approach, described in the previous section, a dynamic CIRS thorax phantom (CIRS, Virginia, USA) mimicing an average human thorax in shape, proportion and composition was utilized. A rod, made out of lung equivalent material, contained a spherical high-density target structure of about 9 mm in diameter and was inserted into the lung equivalent lobe of the phantom. The rod was connected to a motion actuator and a cyclic motion trajectory was predefined. Over one simulated breathing cycle, the motion

range of the spherical high-density structure was 2 cm in sup-inf, 1 cm in ant-post directions and no motion laterally. An ANZAI belt was connected to the phantom surrogate motion platform. A 4D CT of the phantom was acquired and reconstructed into 10 phases. During the 4D CT acquisition breathing cycle of 4 seconds was used.

A monoenergetic quadratic anterior – posterior directed PBS proton field of 115 MeV and 5 cm × 5 cm size was delivered. The energy of the beam was chosen in order to ensure that the protons would pass through the phantom when not passing through the high-density structure and vice versa. The size and position of the field was chosen to cover the entire area of the projected movement of the spherical target structure. The phantom was aligned to the treatment isocentre by using on-board x-ray imaging system. A dosimetric measurement was performed by placing a Gafchromic EBT3 film (Ashland Inc., Covington, USA) posteriorly below the phantom. Two measurements were performed: First, the target was moved with a simulated breathing cycle of 4 s. Secondly, a breathing cycle of 8 s was applied. During the beam delivery the "breathing motion" of the phantom was registered with the ANZAI system. The beam-on time was 2.8 s, therefore only a few pencil beams traversed the spherical high-density structure, resulting in a low dose "shadow" on the Gafchromic EBT3 film. The position of this shadow in respect to the field edges depends on the timing of the beam delivery (scanning) in respect to the timing of the motion of the spherical high-density structure, in other words, on the interplay. The experimental setup is shown in Figure 4.

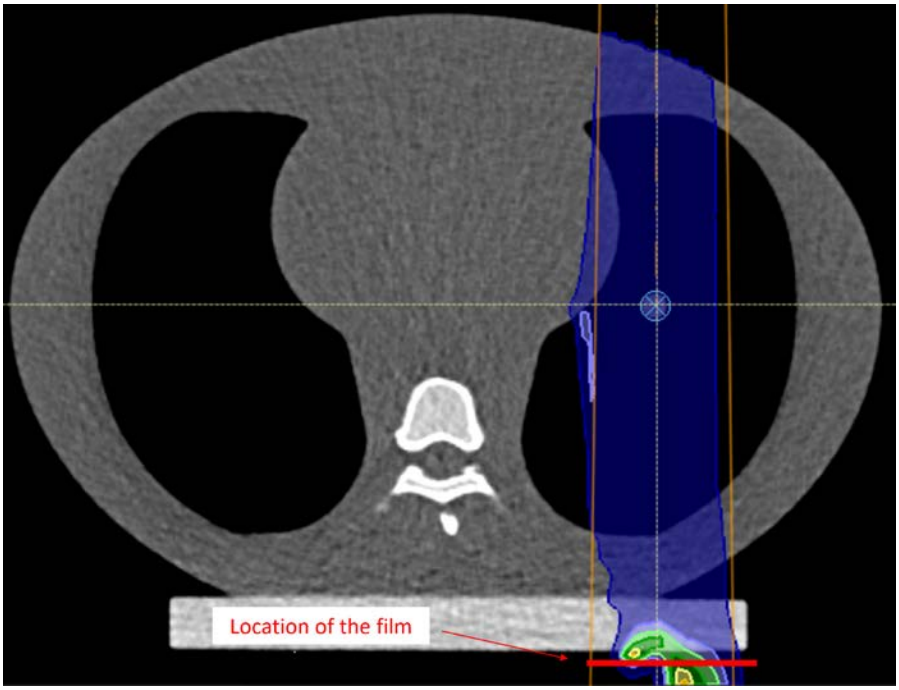

Figure 4: Transversal slice of the dynamic CIRS thorax phantom. An anterior – posterior monoenergetic beam is used to cover the area enclosing the motion range of the spherical target structure. The film is placed posteriorly below the phantom, perpendicular to the beam axis.

To validate the proposed 4D dose reconstruction approach, the dose profiles of the measured films were compared to the 4D reconstructed dose, using the 4D CT, the machine log file and the ANZAI output signal as described in the previous section.

Results

The timeline of the PBS delivery was correlated with a different part of the motion monitoring data for each fraction (Figure 1). The correlation for one exemplary fraction is shown in Figure 5. 33 fraction doses were recalculated using different parts of the ANZAI output files, the six different 4D-CT datasets and machine log file of 33 dry run irradiations. The dose distributions of

the log-based sub-plans and the resulting fraction dose is shown for an exemplary fraction in Figure 6.

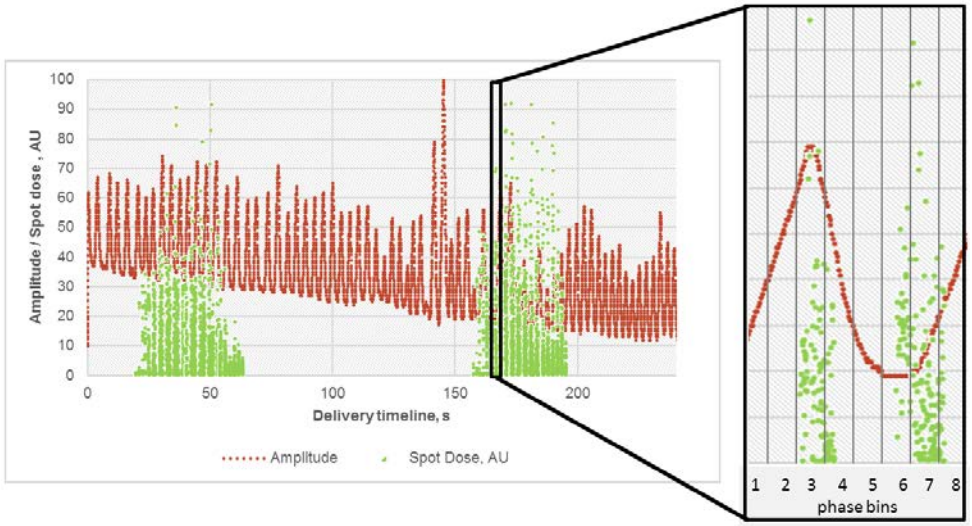

Figure 5. PBS plan delivery timeline based on delivery machine log file (green dots) overlaid on patient's breathing pattern (red dots). On the right, a zoom in can be seen.

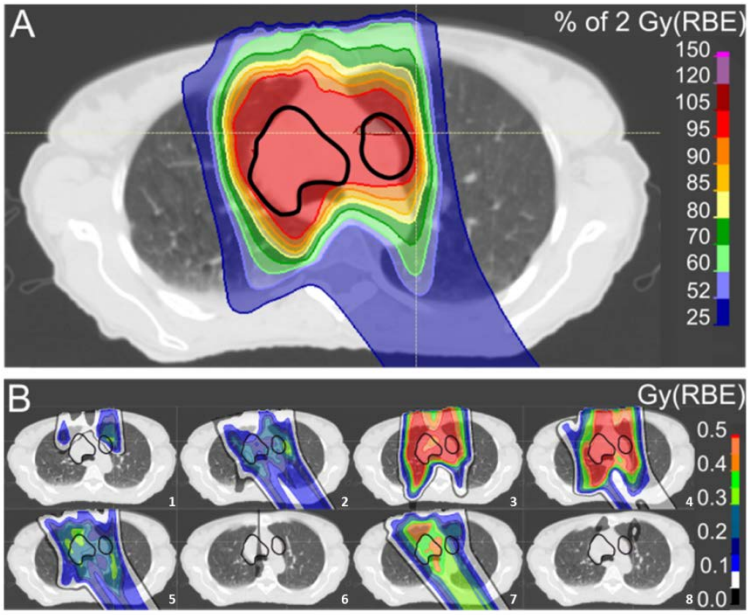

Figure 6: 4D dose of one fraction (A) calculated with the presented method based on sub-plan doses for eight 4D-CT phases (B). CTV is shown in black.

Fraction doses were subsequently accumulated. Figure 7 shows the linear increase of D98 values over the entire treatment course. Following formula [1] projected full treatment course doses were calculated after the delivery of each fraction. After an initial projected increase of D98 values, a drop after fraction 6 was recognized (Figure 7). At fraction 25 the projected D98 values drop below the D98 tolerance level, indicating an under-dosage of the CTV.

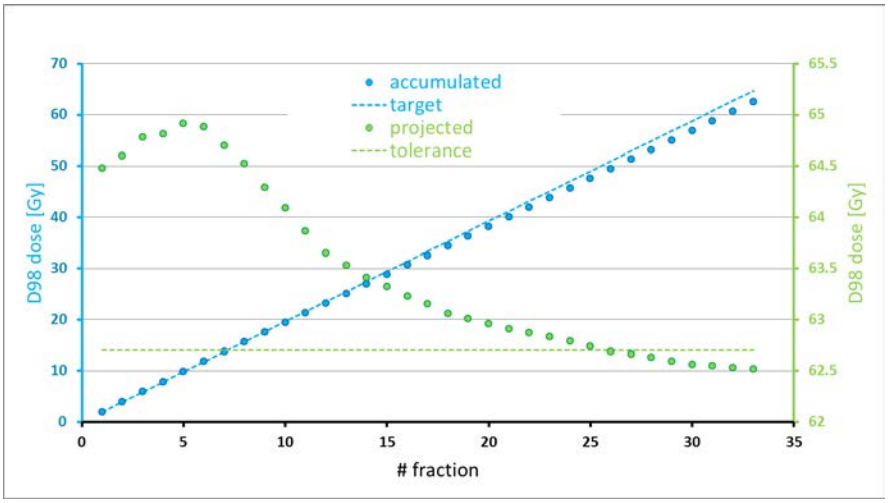

Figure 7: Accumulated (blue) and projected (green) D98 dose after each fraction.

A comparison of the nominal dose distribution, the projected full treatment course dose after 16 fractions and the 33 accumulated reconstructed fraction doses reveals a CTV under dosages of the projected and accumulated dose distribution compared to the nominal treatment dose (Figure 8). Almost no changes in spinal cord dose, mean heart and lung doses were observed.

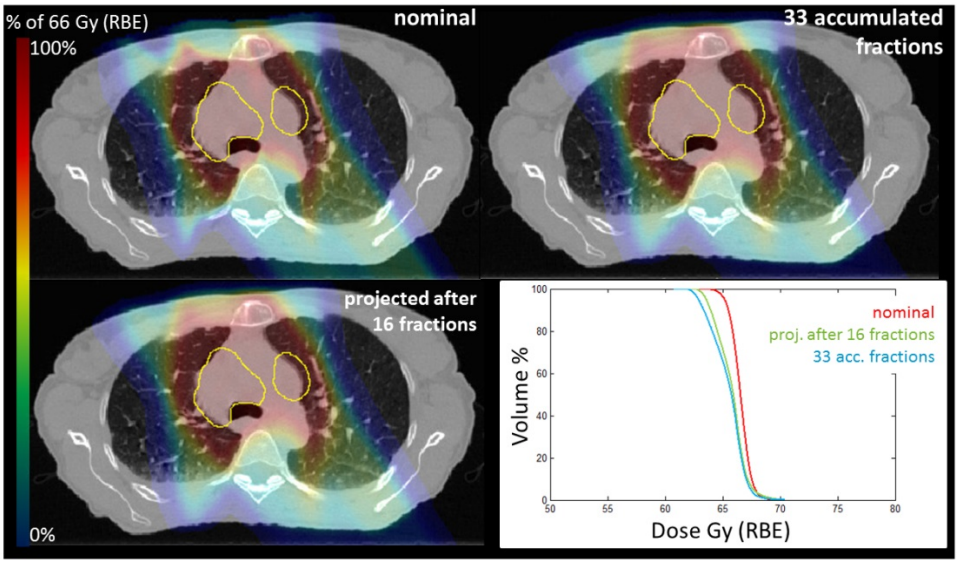

Figure 8: Comparison of nominal dose, the projected dose after delivering 16 fractions and the accumulated dose at the end of treatment course. The CTV in displayed in yellow. On the lower right, DVH plots for the nominal (red), the projected (green) and the accumulated (blue) dose distributions for the CTV can be seen.

Required time for processing of the machine log file and the ANZAI output file was 30 seconds for one fraction. We estimate that these calculations require between 20 and 120 seconds for any arbitrary patient, depending on the number of treatment fields and spots. Sub-plan import and dose accumulation for one fraction takes around 4-8 minutes, depending on the number of sub-plans (or in other words the number of 4D-CT phases). In addition, a manual data preparation is required, namely placing the current input files (log files, ANZAI output) in a dedicated folder and specifying relevant computation settings in a setup file. Calculation of projected course dose or total course dose based on fraction doses need additionally less than five minutes for manual input in RayStation.

Experimental validation

Figure 9 shows a comparison of the Gafcromic EBT3 film measurement and the 4D reconstructed dose. The position of the low dose shadow in respect to the field edges agrees with a millimetric accuracy, demonstrating the accuracy of the proposed 4D dose reconstruction methodology using machine log files and ANZAI output data.

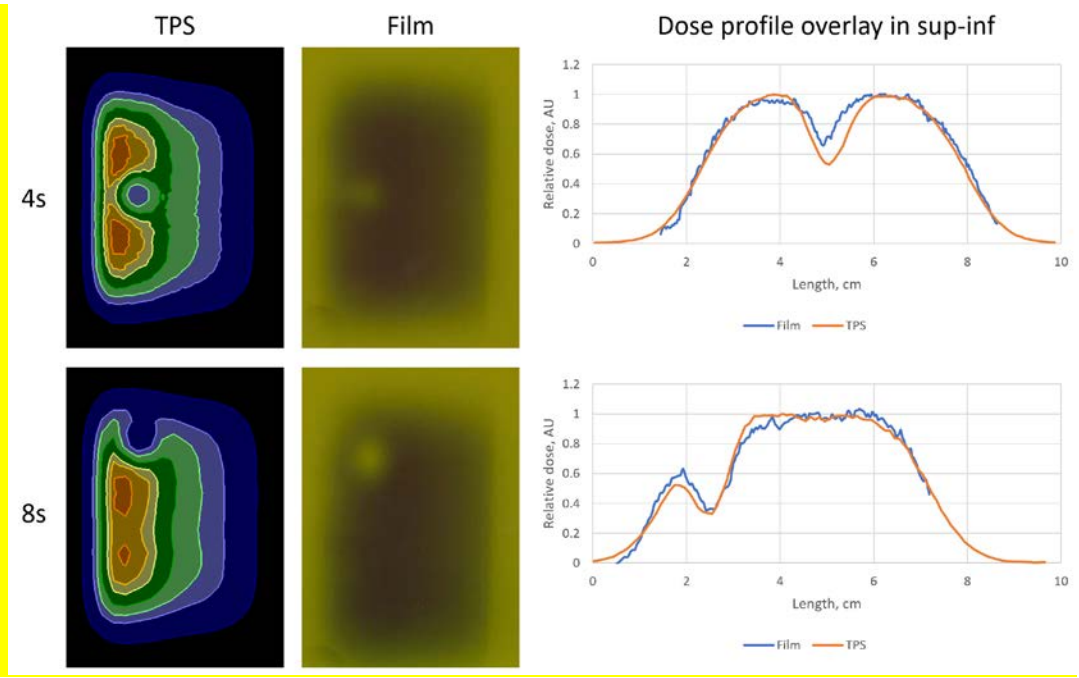

Figure 9: Comparison between dose planes as experimentally acquired on Gafchromic film and as retrieved from 4D reconstructed dose distribution by using treatment delivery log files and motion information monitored with an ANZAI system. Profile analysis shows agreement between position of the target structure as according to the measurement and as according to the 4D dose reconstruction within 1 mm.

Discussion

In this proof-of-concept study, we showed the feasibility of fraction-wise retrospective assessment of the actually delivered dose distribution within a commercial treatment planning system. Our approach incorporates treatment machine log files and recorded breathing patterns for each fraction as well as multiple 4D-CT datasets acquired throughout the treatment course. The 4D dose reconstruction per fraction is performed completely in RayStation 6 via its scripting module. With such an easy-to-use method, the accumulated delivered dose at any time point during the treatment course or a projected full treatment course dose can be quickly assessed by summing up the doses to the current treatment fraction and for the projection, scaling it with the number of total fractions. The accumulated delivered dose or the projected treatment course dose is relevant for monitoring the quality of the treatment delivery while progressing through the treatment and can support decisions regarding the necessity of treatment plan adaptation. The feature of considering actual instead of nominal quantities for tumour motion, beam delivery and the subsequent consideration of the actual interplay cannot be overrated, even if still estimations apply. These are essential contributions to the high-quality implementation of PBS proton therapy of moving targets.

4D dose reconstruction quality

The frequency of the input 4D-CT acquisition has an impact on the dose reconstruction quality. More scans which are acquired as close as possible to the actual treatment will increase the quality of the reconstructed dose. This frequency as well as its off-line nature is a limitation in the precision of dose reconstructions. The main assumption is that the breathing motion pattern and anatomical situation of the patient is the same during image acquisition and treatment, which is not always valid. Using weekly 4D-CT datasets, as in our proof-of-concept study, is a reasonable compromise between the clinically manageable frequency of 4D-CT acquisitions, the additional

imaging dose to the patient and the highest dose reconstruction quality. As the differences in motion pattern and anatomical changes for our exemplary patient case were rather small between the consecutive 4D-CTs, the chosen frequency was sufficient. For other patients another frequency might be appropriate which could be assessed by comparing several consecutive 4D-CT datasets or 4D-CBCTs. The implementation of the script-based dose reconstruction is, however, independent of the number of images, and can be used "as is" including as many images as available. It is also possible to include synthetic daily CT data which could be created based on daily 4D cone-beam CT or magnet-resonance (MR) information [14–16]. These developments aim on the almost or indeed online assessment of motion and anatomical changes. Although this approach would reduce the uncertainty in potentially outdated anatomy and motion data, there is still a lot of translational work to be done like implementing reliable dose calculations for PT based on cone-beam CT and MR, before this could be actually used in a clinical setting.

Additional uncertainty arises from the precision of the applied deformable image registration in RayStation. The vector fields were assessed qualitatively with tools in RayStation and rated as sufficiently precise for the given purpose. It is highly important to evaluate the vector field quality for each deformable image registration to assess the uncertainties introduced in the dose calculation as highlighted in Ribeiro et al. [13]. Quantitative evaluation, however, is largely time consuming and complicated (e.g. based on manually choosing landmarks in both registered datasets) [17] and currently not featured in RayStation.

Current technical issues

A practical limitation in the presented retrospective 4D dose reconstruction is the limited capability of RayStation to work with a large number of dose distributions. This might be avoided, if only fraction doses are used inside RayStation without storing the sub-plan doses, decreasing the number of handled dose cubes by a factor of 9. An adaption by RaySearch to enable the handling of larger amounts of data is desirable.

A difficult step in the general implementation of the retrospective dose assessment is the synchronisation between the time stamps of the treatment machine log files and the breathing curve output of the ANZAI system. Richter et al. described the remaining synchronisation accuracy in their system to be about 250 ms, despite their efforts [8]. This remaining uncertainty had a large influence on the estimated dose distributions, with up to 25% variation in parameters like V_{95} and V_{107} of the target. This underlines the importance of a precise synchronisation process. They concluded that the synchronisation accuracy needs to be better than 25 ms to achieve acceptable 4D dose reconstruction. However, this problem largely depends on the individual software setup and IT infrastructure and needs to be addressed individually in each implementation.

In our approach, we used treatment machine log files from an IBA proton machine and the breathing pattern output from the ANZAI system. However, in principle, the scripts can be adapted to the output of any respiratory motion management system and any log file output. Furthermore, different CT systems use different reconstruction algorithms (in general, phase-based versus amplitude-based reconstruction). The breathing pattern analysis and 4D-CT assignment would need to be adapted to another input system if required. Although, the scripts were implemented for RayStation 6, the adaptation of these scripts to fit the new requirements of RayStation 7 or later should be feasible without major changes.

In summary, the retrospective 4D dose reconstruction and accumulation, now implemented in Groningen and Dresden, allows for an approximation of the actually delivered dose and is an extremely powerful tool in supporting the quality assessment of PBS proton therapy for moving tumours. With a time duration of 10 minutes per fraction assessment, the approach is clinically feasible, contrasting a time consuming prospective 4D evaluations considering a comprehensive parameter space of different organ motions, various interplay scenarios, different anatomical variations and multiple setup scenarios.

In future, the retrospective 4D dose reconstruction and accumulation is foreseen to be used for assurance of the treatment delivery quality and to support decisions on plan adaptation. To enable this, (site–specific) treatment quality indicators and action levels must be defined to trigger plan adaptation if required. One possible adaptation strategy could be the introduction of an additional motion mitigation technique (for example, breath-hold) at a given time point of fractioned treatment, for example when an increasing target motion amplitude would compromise the treatment quality. Alternatively, one could re-optimize the treatment plan using the 4D reconstructed dose as background dose. Any adapted treatment course should then be further monitored, assuring that further deviations shown in the subsequently reconstructed and accumulated 4D treatment are within acceptable margins.

The described proof-of-concept mainly focuses on 4D treatments, however the methodology can be generalized and applied to indications across the body. To reconstruct and accumulate dose for treatment sites not affected or minimally affected by the organ motion, the amount of required input data would simply be smaller and the number of calculations would be decreased.

Conclusion

The development of a 4D-dose-accumulation treatment-assessment tool, now ready for clinical application, allows for assessing the quality of the delivered dose throughout the treatment course, taking appropriate actions, e.g. plan adaptations, in case of significant deviations. We implemented and experimentally validated this tool in a commercially available treatment planning system using its scripting functionality for an easy-to-use procedure feasible in a clinical setting. This is an essential step towards safe clinical implementation of PBS proton treatments for moving targets. In the next step, the general clinical relevance of the approach will be evaluated on a broader patient population and compared to prospective dose evaluations.

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