4D robust optimization in pencil beam scanning proton therapy for hepatocellular carcinoma

T Pfeiler\textsuperscript{1,2}, D Ahmad Khalil\textsuperscript{1,3}, C Bäumer\textsuperscript{1}, O Blanck\textsuperscript{4}, M Chan\textsuperscript{4}, E Engwall\textsuperscript{5}, D Geismar\textsuperscript{1,3}, S Peters\textsuperscript{1,2}, S Plaude\textsuperscript{1}, B Spaan\textsuperscript{2}, J Wulff\textsuperscript{1} and B Timmermann\textsuperscript{1,3}

\textsuperscript{1}West German Proton Therapy Centre Essen, Essen, Germany
\textsuperscript{2}TU Dortmund University, Experimental Physics 5, Dortmund, Germany
\textsuperscript{3}University Hospital Essen, Clinic for Particle Therapy, Essen, Germany
\textsuperscript{4}University Clinic Schleswig-Holstein, Department of Radiation Oncology, Kiel, Germany
\textsuperscript{5}RaySearch Laboratories AB, Stockholm, Sweden

E-mail: tina.pfeiler@uk.essen.de

Abstract. The treatment of moving targets is a challenging task using high conformal radiation techniques such as pencil beam scanning (PBS) proton therapy and requires adequate motion mitigation. Recent guidelines propose 4D robust optimization to mitigate motion artefacts in PBS therapy of thoracic malignancies. However, the availability of dosimetric analyses supporting this recommendation is limited and even non-existing for other tumour sites. The objective of this study was therefore to analyse the effectiveness of 4D robust optimization for hepatocellular carcinoma (HCC), representative for moving abdominal targets. These are usually less affected by uncertainties due to tissue heterogeneities than thoracic targets. 4D robustly optimized plans were compared with beam-specific margin plans for 6 HCC patients based on 4D dynamic accumulated doses (4DDD). 4DDD computations were conducted in RayStation with an experimentally validated routine including a site-specific beam time model. Contrary to expectations based on thoracic studies, 4D robust optimization did not yield a more homogeneous target coverage except for shallow targets close to the ribs. A clear advantage of 4D robust optimization is the sparing of normal tissue. The average dose to the normal liver could be reduced by up to 12%.

1. Introduction

Pencil beam scanning proton therapy (PBS) enables high-precision treatment for malignant tumours due to its steep dose gradients in beam direction. The utilization of the distinctive dose profile of protons in an intensity modulated approach (IMPT) allows sparing of organs at risk (OARs) even for complex anatomies. However, it is exactly this concept that makes PBS particularly susceptible to range uncertainties and organ motion. The interplay of organ motion and beam scanning may cause distortions of the intended dose distribution [1]. In order to exploit the full potential of PBS also for moving targets, motion mitigation techniques like robust optimization and modelling of interplay effects become crucial. Guidelines recently published for thoracic cancer [2] recommend 4D robust optimization to mitigate interplay effects in (intensity-modulated) PBS. However, only few exploratory studies exist [3-5] and dosimetric investigations of 4D robust optimization for different optimization algorithms and tumour sites are lacking, not least because an appropriate, site-specific beam time model is required for 4D dynamic accumulated dose (4DDD) computation. 4DDD...
computation is a prerequisite to evaluate whether the applied motion mitigation technique is adequate. Such a 4DDD tool is currently not available within a commercial treatment planning system (TPS).

This study investigates the potential of 4D robust optimization to reduce interplay effects and spare OARs in comparison to the conventional margin concept for hepatocellular carcinoma (HCC). HCC, which is the second leading cause of cancer related mortality worldwide [6], is selected as a model system for moving targets, because it is less affected by tissue heterogeneities and related range uncertainties than thoracic targets. 4DDD computations were performed with a customized and experimentally validated interplay effect routine in a clinical treatment planning environment [7].

2. Materials and Methods

2.1. Patient data and treatment planning

4DCT datasets from 6 HCC patients enrolled in a previous study [8] were included in the current work. The selective uptake of lipiodol by tumour cells after trans-arterial chemo-embolization was exploited as natural contrast and abdominal compression limited the tumour motion. The maximum motion vector length, defined as the difference between the dimensions of the clinical target volume (CTV) and the internal target volume (ITV), varied between 0.7 cm and 1.3 cm. The tumour size ranged from 3 cm³ to about 500 cm³ (average 160 cm³).

Two-field PBS treatment plans were generated in a research version of RayStation 6 (RaySearch Laboratories AB, Stockholm, Sweden) using the pencil beam dose algorithm and 4D robust optimization based on worst case scenarios (4D plans). A uniform dose of 63 GyRBE (Dpres) was prescribed to the CTV in 15 fractions according to Ref. [9] allowing for intensity modulations within single fields. The robust optimization settings were chosen to achieve plan robustness against 2 mm setup error, 5% range uncertainty and morphological changes in 10 respiratory phases. For comparison purposes, corresponding non-robustly optimized PBS plans were created on the end exhalation phase based on beam-specific planning target volumes using a single field uniform dose approach (SFUD plans). The uncertainty parameters above were used as margins in this case, whereby the internal margin (accounting for target motion) was derived from 10 respiratory phases. For both, 4D and SFUD plans, the energy layer spacing and the spot distance were set automatically with a scale factor of 1.1 and 0.8, respectively. The energies ranged from 100 MeV to 195 MeV, whereby range shifters were applied, when necessary. The air gap between a range shifter and the patient varied from 2 cm to 5.4 cm.

2.2. Interplay effect evaluation

An interplay effect routine tailored to 4DDD computations of irradiations with an IBA Proteus®Plus proton therapy system (IBA, Louvain-La-Neve, Belgium) in RayStation forms the basis for all plan analyses as described in a former project [7]. The time structure of the field delivery is provided by an empirical beam time model and used to determine the delivery start time of a beamlet (spot). Based on the specified respiratory cycle length and starting phase of the irradiation, the application of each spot can be assigned to one of the respiratory phases of the 4DCT. For every phase i, a fraction dose \( d_{fx,CT} \) is calculated and subsequently mapped to the reference phase \( j \) using the ANAtomically CONstrained Deformation Algorithm, ANACONDA [10]. The summation over all deformed doses \( d_{fx,CT}^{ref} \) and the dose delivered within the reference phase \( d_{fx,CT}^{ref} \) yields the fractional ‘interplay dose distribution’

\[
 d_{fx} = a_{fx,CT1}^{ref} + a_{fx,CT2}^{ref} + \ldots + a_{fx,CTR}^{ref},
\]

where \( fx \) indicates the fraction number and \( r \) the total number of respiratory phases. The total delivered dose \( D \) is given by the sum over all fraction doses:

\[
 D = \sum_{fx=1}^{N} d_{fx}.
\]

The outcome of a single fraction was analysed based on 60 simulations per plan with varying starting phases and energy layer switching times in accordance with Ref. [7]. A whole treatment course, consisting of 15 fractions, was modelled with a reduced set of 5 simulations per fraction (75 simulations per plan). The homogeneity index \( HI = (D_5 - D_{95})/D_{pres} \) and the percentage over-
underdosage $V_{107,95} = V_{107} + (100 - V_{95})$ served as evaluation criteria due to their sensitivity to interplay effects. For all evaluations, a constant respiratory period of 4 s was chosen.

Figure 1. Single fraction 4D dynamic accumulated dose for a 4D robustly optimized plan (a) and a non-robustly optimized plan (b) (coronal view).

3. Results

Figure 1 shows exemplarily the coronal view of a 4DDD distribution of a single fraction for a 4D and a SFUD plan. For a single fraction, the HI of the CTV was on average 9.2% for 4D and 8.8% for SFUD plans. The standard deviation (SD) varied from 0.6% to 2.1% (4D) and 0.8% to 1.7% (SFUD), respectively (see Fig. 2). 4D plans exhibited on average a $V_{107,95}$ value of 5.9% within the CTV and SFUD plans 5.0%. The corresponding SD ranged from 1.2% to 5.6% (4D) and 2.2% to 4.1% (SFUD), respectively. No correlation between the size of the CTV or the motion amplitude and the severity of interplay effects was found. Slightly smaller HI and $V_{107,95}$ values were observed for 4D plans when the CTV was located close to the ribs whereas SFUD plans yielded better 4DDD results for centrally-located targets in the liver (see Fig. 2).

OARs close to the target, such as ribs and the healthy liver tissue, could be better spared when using 4D robust optimization (see Fig. 1). For shallow targets, the rib volume receiving more than 60 GyRBE was on average 8 times larger for SFUD plans than for 4D plans leading to a probability of rib fracture of up to 6.3% according to Ref. [11]. The average dose to the healthy liver tissue could be decreased by 0.6% to 12.0% (average 6.9%) with 4D robust optimization.

Simulating the whole treatment course over all fractions, the HI decreased to less than 5% for both treatment techniques as can be seen in Fig. 2. The average HI of 3.2% (4D) and 3.1% (SFUD) was only a little higher than for the static case (2.0% and 2.1%). $V_{107,95}$ approached 0% in all cases.

4. Discussion

On average, the interplay effect was slightly less pronounced for SFUD plans than for 4D plans. The reason is presumably the larger volume covered by 95% of $D_{\text{pres}}$ in SFUD plans than in 4D plans (average 18.8%). This potentially reduces the over- and underdosage at the edge of the CTV. Further, SFUD plans exhibit a uniform dose per field and inhomogeneities in one of the fields might be better compensated which is expected to improve robustness against motion. However, for shallow targets (1, 3 and 5 in Fig. 2), 4D plans led to slightly more homogeneous target coverage. Here, the 4D optimization algorithm avoided irradiation through the ribs and CTV regions directly behind the rib were covered by the other field.

The study demonstrated that 15 fractions were sufficient to mitigate interplay effects within the CTV for both 4D and SFUD plans. The dose to normal tissue could be significantly reduced in 4D plans since robust optimization adjusts the irradiation volume to density changes unlike the more conservative margin concept. The advantages (better OAR sparing and slightly less interplay effects for shallow targets) and disadvantages (slightly stronger interplay effects for centrally-located targets and long computation times) of 4D robust optimization must be weighed up on a case by case basis.
Treatment planning options that were not specifically addressed in this study - but have the potential to further mitigate interplay effects within a single fraction - are a larger number of treatment fields, rescanning and the increase of the air gap between range shifter and patient to enlarge the spot size [12]. This would be at the expense of treatment time and a sharp lateral dose fall-off.

All 4DDD computations rely on the respiratory motion information derived from planning 4DCTs and might lose their validity if motion trajectories changes occur during treatment. As a consequence, great care should be taken when transferring knowledge from research to clinic where individual 4DDD evaluations based on a planning 4DCT might lead to a false sense of security.

5. Conclusion
Using the specified uncertainty criteria, 4D robust optimization was not found to be superior to the conventional margin concept in terms of reducing interplay effects for the HCC patients under consideration. In the case of centrally-located targets, HI and V_{107.95} were even slightly better for non-robustly optimized plans considering a single fraction. However, in the case of shallow targets close to the ribs, 4D robust plans were shown to be slightly beneficial in terms of target coverage. Moreover, robust optimization reduced the 4DDD to close-by OARs which can be of importance for critical cases. The study showed that dose inhomogeneities were averaged out for the applied fractionation scheme of 15 fractions for both treatment planning techniques. The results could differ for patients treated under other conditions, e.g. without abdominal compression or lipiodol contrast. This needs to be further investigated in a larger patient cohort.

6. References
[1] Bert C et al 2011 Phys. Med. Biol. 56 R113-44
[2] Chang J Y et al 2017 Int. J. Radiat. Oncol. Biol. Phys. 99 41-50
[3] Liu W et al 2016 Int. J. Radiat. Oncol. Biol. Phys. 95 523-33
[4] Newpower M et al 2016 Med. Phys. 43 3504-5
[5] Yu J et al 2016 Med. Phys. 43 1111-8
[6] Ferlay J et al 2015 Int. J. Cancer 136 E359-86
[7] Pfeiler T et al 2017 Z. Med. Phys. 28 121-33
[8] Chan M K et al 2016 Strahlenther. Onkol. 192 92-101
[9] Bush D A et al 2011 Cancer 117 3053-9
[10] Weistrand O et al 2015 Med. Phys. 42 40-53
[11] Kanemoto A et al 2013 Acta. Oncol. 52 538-44
[12] Grassberger C et al 2013 Int. J. Radiation. Oncol. Biol. Phys. 86 380-6