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Tumor motion

Impact of fractionation and number of fields on dose homogeneity for intra-fractionally moving lung tumors using scanned carbon ion treatment

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ABSTRACT

Background and purpose: Scanned particle beam therapy may result in over and under dosages within the target volume. This study quantifies how CTV dose coverage improves with number of fractions and fields.

Materials and methods: Based on 4DCTs of nine lung tumor patients, treatment plans were optimized separately for four different fields using an ITV approach. 4D RBE-weighted dose distributions were calculated for varying motion parameters and fraction numbers. The total RBE-weighted dose was determined for one and four-field application per fraction. DVHs were analyzed for the tumor and interpreted based on statistical modeling.

Results: Dose homogeneity within the CTV increased with the fraction number, but depends significantly on the tumor motion amplitude. For single-field schedules and amplitudes >6 mm, the dose coverage indices ($V95_{min}$ = 90.7% and $V107_{max}$ = 0.4%) differed to the stationary case even after 40 fractions. Target coverage for a four-field approach followed a proposed model and homogeneous dose distributions could be achieved 6-times faster than single-field treatments.

Conclusions: Fractionated delivery improves dose homogeneity in scanned ion beam therapy of moving targets. The achievable homogeneity depends mainly on tumor volume and motion amplitude. The outcome of multiple-field irradiations can be predicted based on single-field results and accelerates the achievement of homogeneous dose distributions.

Radiotherapy is one treatment option for pulmonary tumors, especially if inoperable with clinical surgery. Hypo-fractionated irradiation with carbon ions offers a benefit in terms of biological efficiency, sparing of healthy tissue and treatment time compared to conventional photon therapy [1]. A number of studies showed promising results for hypo-fractionated treatment of non-small-cell lung cancer (*NSCLC*) with passively shaped carbon ion beams [2]. However, for the treatment of tumors with intra-fractional motion using scanned ion beams, interferences between target and beam spot motion can result in clinically relevant over and under dosages within the clinical target volume (*CTV*) [3]. A few institutes are treating liver or lung tumors using a scanned beam combined with abdominal compression or apnea, respectively in order to mitigate these interplay effects [4,5]. Irradiation of moving tumors with larger motion amplitudes becomes more complex, so additional techniques have been developed in the last years [3] but are currently not readily available for scanned particle beam treatments, even though the Paul Scherrer Institute (*PSI*), Villigen, Switzerland, are expected to start patient treatments with rescanning. Rescanning relies on averaging effects of multiple irradiations of an internal target volume (*ITV*) with a proportionally reduced dose [6–8]. From a target motion perspective volumetric rescanning is comparable to fractionated treatment or treatments with multiple fields [9] but radiobiological aspects change and have to be quantified appropriately.

The aim of this study was to investigate the impact of (hypo-) fractionated delivery on dose homogeneity in scanned carbon beam therapy, i.e. the potential to interpret fractionated treatment

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as a motion mitigation technique. Dose coverage within the CTV in dependence on the number of fractions for two different field application methods was studied considering the increased biological effectiveness of carbon ion beams compared to conventional photon therapy. Furthermore, the minimum number of fractions and fields to achieve the required homogeneity was examined. The analysis did not include organs at risk (*OAR*) since specific biological base data for these tissues are currently not available.

Materials and methods

Patient data

At the MD Anderson Cancer Center (*MDACC*) in Houston, TX, lung tumor patients were treated with scattered beam proton therapy and intensity modulated radiation therapy (*IMRT*). For this study, anonymized four-dimensional computed tomography (*4DCT*) data sets, with ten motion states have been used from nine MDACC patients with NSCLC, squamous-cell carcinoma (SCC) and adenocarcinoma within an Institutional Review Board (*IRB*) approved protocol. In a reference phase (end-exhale) the gross tumor volume (*GTV*) and the CTV have been contoured. For further details, including CTV volume and motion characteristics, the reader is referred to the Supplementary material (Supplementary Table 1).

4D treatment plan optimization

Treatment plans were optimized using the GSI in-house therapy planning system *TRiP98* (*TReatment plannIng for Particles*) [10,11] that was used clinically for more than 400 patients [12]. A 4D-extension was implemented in the last years and validated against experimental data [13]. This version allows calculation of the relative biologically effective dose delivered by pencil beam scanning in the presence of respiratory motion based on 4DCTs, transformation fields, motion surrogates and the scanning process determined by the beam extraction profile.

For this study, transformation fields were determined by the open source software *Plastimatch* using a B-spline algorithm [14] to establish the voxel correspondence between the respiratory phases. Based on this registration, the motion of the tumor and the surrounding tissue can be described by a set of 3D transformation fields. These fields were used to propagate the CTV from the reference phase to each motion phase forming the ITV. Due to the range sensitivity of charged particles, the geometric union of propagated CTVs is not sufficient to achieve acceptable dose coverage. Rather the union of the water-equivalent path length has been used, which is inherently dependent on the beam direction [15].

Taking into account that gantries are typically not available for carbon beam therapy, beam entrance channels of +20°, −20°, −70° and −110° were chosen corresponding to a 0° and 90° beamline in combination with a 20° couch roll, related to a standard protocol for scattered carbon beam treatment. Each field was optimized individually according to a single-field uniform dose approach as illustrated in Fig. 1a.

RBE approach

The optimization process took the relative biological effectiveness (*RBE*) of carbon ions for NSCLC and healthy tissues into account. The method used at GSI to determine the applied dose accounts for the complex radiation field delivered to the tissue and is based on sets of RBE values for each particle type and energy component [16]. This information is provided by the Local Effect Model (*LEM*) [17,18].

To reveal appropriate input parameters for RBE calculation, parameters were used that result in comparable depth dose distributions as applied in Kanai *et al.* 2006 [19] for scattered carbon beam treatment. However, the actual choice of RBE information does not have a qualitative impact on the results considered in this work and hence, details for the determination of the RBE base data are presented in the Supplementary material. The photon Linear-Quadratic-Linear (*LQL*) parameters used as input data for the LEM to predict the needed RBE information show an α/β ratio of 6 Gy.

Fractionation scheme

In several dose escalation studies, Miyamoto *et al.* reported the clinical feasibility of hypo-fractionation from 18 fractions to single-fraction radio-surgery [20–22]. Generally, altered fractionation schedules include changes in dose per fraction, time interval between subsequent fractions, overall time and total dose. Schedules with 4 fractions per week were chosen along with appropriate doses for 4–40 fractions. Each schedule was simulated twice: for one field and for the application of all four fields per fraction. Fractionation schemes were only calculated for multiples of four fractions in order to balance the influence of individual fields to the dose statistics. To design adequate fractionation schemes for carbon ions, RBE-weighted fraction doses d for 4–40 fractions were determined for a desired value of 90% tumor control probability (*TCP*) using the equation and parameters obtained by Kanai *et al.* [19] for all kinds of tumor diseases. Further information is given in the Supplementary material. Each field was optimized to obtain a uniform RBE-weighted dose distribution.

The total dose distribution after n fractions was obtained by the sum of the dose per fraction for each voxel within the target volume. A summary of the considered fractionation schedules, including overall time, dose per fraction d and total dose D is also listed in the Supplementary material (Supplementary Table 2).

Simulation parameters and data analysis

Based on the optimized treatment plans for each fractionation scheme, 4D dose calculations for various breathing periods T and starting phases φ^0 have been performed to simulate the effect of the fractionated treatment course. For all calculations, a simulated beam extraction profile was used by fitting a Gaussian distribution to several measured extraction profiles from the GSI synchrotron with a pulse length of 2.2 s and a pulse-to-pulse time of 5.5 and 4.5 s for subsequent pulses with and without changes of iso-energy slices (*IES*), respectively.

The external motion surrogate was simulated using the parameterization of Lujan *et al.* [23] to arrange the single phases of the 4DCT and to correlate the beam to the internal motion. The breathing periods, which were in a 3–5 s range according to Seppenwoolde *et al.* [24], as well as the starting phases (0–2π), were selected randomly for each field application. As breathing patterns might not change excessively within one fraction, in terms of the four-field application only one randomly chosen period was used for all four beams of that fraction together with different starting phases.

For each fractionation scheme, ten possible outcomes for different parameter sets of T and φ^0 were simulated using step sizes of $T = 0.1$ s and $\varphi^0 = 1°$. All resulting dose distributions were visually inspected and data analysis focused on Dose–Volume–Histograms (*DVH*). From the DVHs, CTV subvolumes receiving at least 95% (*V95*) and 107% (*V107*) of the prescribed total RBE-weighted dose were calculated. To measure the dose homogeneity within the CTV, the D5D95 value was determined, representing the difference between the dose delivered to 5% and 95% of the CTV [9].

To compare different patients and application methods and to consider sufficient dose coverage, an ε_{95}-index was introduced,