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Particle beam therapy for lung cancer

Reproducibility of target coverage in stereotactic spot scanning proton lung irradiation under high frequency jet ventilation

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ABSTRACT

Purpose: To investigate scanned-beam proton dose distribution reproducibility in the lung under high frequency jet ventilation (HFJV).

Materials and methods: For 11 patients (12 lesions), treated with single-fraction photon stereotactic radiosurgery under HFJV, scanned-beam proton plans were prepared with the TRiP98 treatment planning system using 2, 3–4 and 5–7 beams. The planning objective was to deliver at least 95% of the prescription of 33 Gy (RBE) to 98% of the PTV. Plans were subsequently recomputed on localization CT scans. Additionally, for selected cases, the effects of range uncertainties were investigated.

Results: Median GTV $V_{98\%}$ was 98.7% in the original 2-field plans and 93.7% in their recomputation ($p = 0.039$). The respective values were 99.0% and 98.0% ($p = 0.039$) for the 3–4-field plans and 100.0% and 99.6% ($p = 0.125$) for the 5–7-field plans. CT calibration uncertainties of ±3.5% led to a GTV $V_{98\%}$ reduction below 1.5 percentual points in most cases and reaching 3 percentual points for 2-field plans with beam undershoot.

Conclusions: Through jet ventilation, reproducible tumor fixation for proton radiotherapy of lung lesions is achievable, ensuring excellent target coverage in most cases. In few cases, non-optimal patient setup reproducibility induced density changes across beam entrance channels, leading to dosimetric deterioration between planning and delivery.

Stereotactic body radiotherapy (SBRT) is an established alternative to surgery for medically inoperable early stage (T1–2) non small cell lung cancer (NSCLC) and lung metastases, yielding high 5-year local control rates of 70–90% and low toxicity rates with usually less than 5–8% severe toxicity (grade III) [1–2]. SBRT involves highly conformal, single-fraction or hypofractionated treatments using (non-coplanar) multiple-field techniques that aim at delivering an ablative dose to the tumor, while sharp dose gradients enable sparing of surrounding normal structures. Inherent to the technique is high precision of dose delivery even in moving targets.

Application of proton beam therapy, with its accurate dose localization, has the potential to minimize dose to the lungs and organs at risk as demonstrated in numerous dosimetric comparison studies [3–5], even if compared to very advanced photon techniques [6]. Hence, it is expected to reduce side effects, posing as alternative to SBRT, for early but also more advanced inoperable NSCLC cases, where tolerances of normal structures may limit application of a curative photon dose [7]. Recent retrospective series have shown, that high-dose hypofractionated proton therapy for peripherally and centrally located NSCLC achieves excellent outcomes in terms of local tumor control and safety profile [8]. A phase I trial including also advanced disease has recently proven hypofractionated proton radiotherapy to be well tolerated [9].

However, efficacy and tolerability of proton therapy in comparison to current standards is not yet proven in clinical trials [7,10–12]. This is partly due to the limited number of clinical particle therapy facilities, but also due to challenges in the technical implementation of particle therapy in lung tumors, especially management of tumor motion. The risk of target miss due to organ motion and deformation is expected to be greater in particle therapy than in photon therapy due to the finite particle range, which is typically addressed by extended distal and proximal margins. Additionally, the interplay of target motion and beam scanning renders extra complexity to the irradiation of lung tumors [13]. For this reason, a margin-based approach through the definition of an internal target volume (ITV), encompassing the tumor position in all phases of the respiratory cycle, might not be sufficient to ensure adequate and homogeneous target coverage.

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Various solutions to counteract motion interplay effects have been proposed, for instance gating, tracking, and re-scanning, and their clinical applicability is under active investigation. In contrary, other approaches, like apnea and high frequency jet ventilation (HFJV), aim at target fixation [13]. HFJV is a modality of mechanical ventilatory support, which utilizes a respiratory rate greater than the normal value (>150 breaths per minute) and very small tidal volumes, thus preventing any movement of the tumor with respiration [14–17]. The interest of target fixation techniques in particle therapy of the lung lies not only in the expected target volume reduction, but also in managing the sensitivity of particle range to density changes in the beam entrance channels. However, if HFJV is to allow a margin-based planning approach for particle irradiation in the lung, it must be reproducible, since this procedure has to be repeated at least twice, i.e., for the planning computed tomography (CT) acquisition and later for the actual irradiation(s).

The goal of the present work was to investigate the reproducibility of the delivered proton dose distribution under HFJV by means of a planning study based on delivery-time localization CT scans from patients who were treated with photon SBRT under HFJV.

Materials and methods

Patient data

Datasets of 11 patients with 12 lesions were selected. All patients were treated for peripheral stage I NSCLC (9 patients) or metastases (2 patients), within an experimental protocol, with single-fraction stereotactic radiosurgery, to up to 33 Gy isocenter dose, under HFJV at the St. Marien-Krankenhaus [15–16]. According to the institutional protocol, patients qualify to receive treatment under HFJV, if the target motion amplitude exceeds 1 cm [15–16]. The HFJV is performed with pulse frequency of 300–400 times a minute, inducing virtually complete standstill of the lung [15–17] (see movie in electronic Supplementary material).

All patients received two CT scans, both under HFJV and immobilized in a vacuum mattress combined with a stereotactic body frame: one as planning CT and the second for target localization verification on the day of irradiation. Localization CT datasets were restricted longitudinally to the slices encompassing the tumor region.

Delineation of relevant structures was performed with the Pinnacle^3 (version 8.0; Philips Radiation Oncology Systems, Best, The Netherlands) treatment planning system on both planning and localization CT. The planning target volume (PTV) was defined by isotropic 3D expansion of the gross tumor volume (GTV) by 5 mm. Median (range) GTV and PTV volumes were 6.7 (1.0–22.9) cm^3 and 24.6 (7.2–71.5) cm^3, respectively. Subsequent to contouring, for each lesion, rigid coregistration of both CT datasets was performed with focus on the tumor region.

Treatment planning

Using the original planning CTs, scanned-beam proton treatment plans were prepared with the TRiP98 treatment planning system (GSI, Darmstadt, Germany) [18]. The total prescription dose was 33 Gy (RBE) and the planning objective was the delivery of at least 95% of such prescription to 98% of the PTV, while, owing to the peripheral localization of all lesions, no normal tissue optimization constraints were deemed necessary. For each patient, three treatment plans were prepared: (a) a plan using two coplanar fields entering the patient ipsilaterally at 0° and 45° in compliance with the fixed nozzles (horizontal and oblique) installed at the Marburg Ion Therapy center (MIT), (b) a plan using 3–4 fields (similarly to [19]) and (c) a plan using 5–7 fields (similarly to [6]), the latter two representing increasing degrees of freedom offered by additional fixed beam lines, patient positioning solutions or a rotating gantry.

Non-coplanar beam setups were excluded because of the limited longitudinal extent of the localization CTs. Plans were optimized for a nozzle-to-treatment-isocenter distance of 60 cm, as available at the MIT center to reduce excess spot size enlargement stemming from the proton beam divergence [20]. Single-field-uniform-dose optimization was used, for its expected lower sensitivity to delivery-time uncertainties in comparison to intensity modulation (IMPT) [21].

The irradiation raster pitch was set to 3 mm, while available spot sizes, at the energies required by the cases under investigation, ranged from 6 to 18 mm full-width-half-maximum (FWHM). Further optimization parameters, expressed in beam's eye view coordinates, were an in-depth spot positioning step of 2 mm and a lateral allowance in placing spots outside the PTV of 1.5 times the spot size.

Successive delivery of the optimized proton plans was simulated by forward-recomputing them on the coregistered localization CT scans.

Additionally, in order to investigate delivery stability in presence of range uncertainties, for the two patients with the least and most deeply seated tumors in the cohort, all plans were recomputed introducing systematic CT calibration errors of ±3.5% [5,22].

Evaluation

The original and recomputed treatment plans were compared in terms of dose distributions and dose–volume histograms (DVH). For a quantitative assessment, different dosimetric parameters were employed: the percentage of the PTV receiving at least 95% of the prescription dose ($V_{95\%}$), and similarly $V_{95\%}$ and $V_{98\%}$ of the GTV. For statistical comparisons a two-sided sign test was performed with a significance level of 0.05 (with Bonferroni correction) using the *R* statistical environment [23].

Results

Dosimetric quality of the optimized plans

The PTV $V_{95\%}$ was >98% for all patients in all plans, without statistically significant differences between planning techniques, and normal tissue dose–volume indexes were below recommended reference values [24] (Table 1). Exceptionally, recommended limits were exceeded for the chest wall in individual cases because of inclusion in the PTV, independently of the planning approach, while its median population value could be reduced through use of more than 2 fields. This in turn resulted in significantly increased involvement of the ipsilateral lung. As only patients with peripheral tumors were included, organs like liver, spine, esophagus and trachea received very low doses (Table 1, structures with median $D_{\text{near-max}} = 0$ not shown), independently of the planning technique.

Qualitative reproducibility assessment

Concerning anatomical reproducibility in the localization CTs, even if patient setup was performed with stereotactic precision, in few patients changes due to repositioning were observed e.g., arm mispositioning or slight body rotations. Tumor position reproducibility was in general very good.

Fig. 1 shows an example of registration results for two patients (a and b), as well as Hounsfield unit (HU) profiles along the central