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Particle therapy in lung cancer

Adaptation is mandatory for intensity modulated proton therapy of advanced lung cancer to ensure target coverage

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ABSTRACT

Background and purpose: Large anatomical changes during radiotherapy are seen for a large proportion of lung cancer patients. We investigate the applicability of a decision support protocol for photon therapy in a proton therapy setting.

Material and methods: Twenty-three consecutive NSCLC patients treated with adaptive photon therapy were retrospectively planned using IMPT. The adaptive protocol was based on geometrical measures of target positioning and large anatomical changes as shown on daily CBCT scans. Two surveillance CT-scans were acquired during the treatment course. The consequences of anatomical changes were evaluated by recalculating the proton plans on the surveillance scans. The CTV receiving 95% of the prescribed dose was analysed.

Results: Fourteen (61%) patients needed adaptations when treated with protons, given that 95% of the CTV must be covered by 95% of the dose. In comparison, no patients needed adaptation when treated with photons using this criterion. The adaptive protocol was found to identify patients with large target under-dosage for proton therapy (six patients). Additionally, target under-dosage was observed for eight patients with non-rigid changes up to 15 mm in the positioning of the bones.

Conclusions: Proton therapy for loco-regional lung cancer demands daily imaging and therapy adaptation for a high proportion of patients.

High rates of local recurrence and toxicity are still predominant in patients with locally advanced non-small cell lung cancer (LA-NSCLC) even with improvements in chemoradiation over the last decades [1]. Radiation of large volumes of lung tissue leads to pneumonitis in many patients treated with photon radiotherapy [2]. Similarly, doses to the heart may contribute to fatal toxicity [3]. Proton therapy has the potential for lowering doses to these crucial tissues with either passive scattering proton therapy (PSPT) [4] and even more so with intensity modulated proton therapy (IMPT) [5–7]. Results from clinical phase I/II studies show low toxicity rates [8–9].

Numerous uncertainties in treatment delivery contribute to deviations between planned and delivered dose. Furthermore, anatomical changes, such as atelectasis, pleural effusion, and differential motion of malignant lymph nodes and primary tumour, are frequent [10–13]. These potentially lead to large deviations in target coverage. In photon radiotherapy (RT) the deviations between planned and delivered dose can be handled through daily imaging with set-up to the target [14], adaptive radiotherapy (ART) that corrects for large inter-fractional errors, and margins accounting for all minor deviations. ART [15–17] restores the planned target coverage in the presence of anatomical changes by creating a new treatment plan for the changed anatomy. Clinical implementation of ART for photons based on geometrical trigger criteria [10,12] has been shown to identify patients needing plan adaptation [18] with a significant decrease in local recurrence rate [19].

Due to the finite range of the proton beam [20–21], the proton dose distributions are more sensitive to density changes resulting in far more severe effects of uncertainties on the dose distribution during treatment [8,22–25] This may undermine the apparent benefit of proton treatment. Hence, the photon concept with margins accounting for minor uncertainties and ART correcting for larger errors may not be transferable to proton therapy (PT), as the association between geometric changes and the resulting dosimetric consequences differs. This association is partly considered in Robust Optimisation [26–27] which incorporates anticipated changes during the PT course into treatment planning. Robust optimisation therefore requires a priori models of the uncertainties that need to be compensated. This leaves some room for ART in case of unforeseen or unlikely geometric changes.

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In this study, we investigate the applicability of a decision support protocol for photon therapy in a PT setting. We address the impact of uncertainties in patient positioning and anatomy on the delivered PT dose distribution and discuss if some of these uncertainties could be included in robust optimisation. We compare PT with IMRT both in terms of reduced dose to organs at risk (OARs) at the planning stage and the actual loss in target coverage during treatment. We investigate to what extent the reduced coverage could be compensated by increasing the prescribed dose, without losing the benefits of PT.

Material and methods

Patient data and target definition

Twenty-three consecutive patients with LA-NSCLC treated with photon radiotherapy were included in the study. The cohort consisted of 10 females and 13 males with a median age of 69 years [53–86 years]. They were staged as IB (2 patients), IIB (1patient), IIIA (10 patients), IIIB (8 patients) and IV (2 patients). The patients received 3 cycles of cisplatin/carboplatin and vinorelbine concomitantly with radiotherapy. The internal gross tumour volume (iGTV) was delineated on the mid-ventilation phase of a planning 4D-CT (pCT) scan with 3 mm slice thickness accounting for respiratory motion for tumour and malignant lymph nodes [28–29]. A subsequent free-breathing ^{18}F-FDG-PET scan was used to guide delineation. The clinical target volume (iCTV) was created by adding a 5 mm expansion cropped with respect to bones and large blood vessels. The median iGTV and iCTV size in the cohort was 93.4 cm^3 [14.5–286.3 cm^3] and 190.3 cm^3 [32.6–438.5 cm^3], respectively.

Margins, setup and adaptive strategy

For photon therapy, the clinical iCTV-PTV margins (anterior–posterior, left–right, superior–inferior) were 4, 4, 5 mm and 9, 9, 10 mm for the tumour and the lymph nodes, respectively [30]. These margins were calculated based on all systematic ($\sum$) and random errors (σ) quantified in the clinical setting at Aarhus University Hospital and included errors due to inter- and intrafractional baseline shifts and deformations, delineation, and machine uncertainties [31]. The patients were set up using daily cone-beam CT (CBCT) imaging with soft tissue match on the primary tumour [18].

An adaptive decision support protocol based on geometrical measures was used for treatment [18], requiring adaptation when deviations in tumour and lymph node position exceeded 2 mm and 5 mm, respectively, for three consecutive fractions, as measured on daily online CBCT images before treatment. Deviations in the position of soft tissue in the mediastinum should be <10 mm. Changes in atelectasis or pleural effusion triggered adaptation. The protocol ensured full target coverage during the treatment course [18].

Proton treatment plans were retrospectively generated based on the same iCTV-PTV margins for expedited comparison [32].

Photon and proton treatment plan comparison

Photon treatment plans were created as 5–8 fields 6MV IMRT plans using the AAA algorithm [33] in the Eclipse treatment planning system (TPS) (Varian Medical Systems) delivering 66 Gy/33 fractions (F) with a homogenous target coverage (95–107%). Constraints for the maximum volume receiving x Gy (V_{xGy}) or the maximum dose to x cm^3 (D_{xcm3}) were applied to the lungs (V_{20Gy} < 35%, mean < 19 Gy), heart (V_{50Gy} < 20%), oesophagus (D_{1cm3} < 66 Gy) and spinal cord ($D_{0.05cm3}$ < 45 Gy). The patients were positioned with both arms above the head in a standard or an individualised immobilisation device.

Multi-field optimised IMPT plans were created in the Hyperion TPS. The software utilises an advanced pencil-beam algorithm with sub-spot decomposition which performs well in heterogeneous media [34]. Proton spot beams were aligned on a rectangular scanning grid with 3 × 3 mm scanning pattern and 2 MeV energy layer spacing. The spot size (sigma) in air at the isocentre was 4 mm. The spot size (sigma) in air at the isocentre was 4 mm at 240 MeV and became larger for lower energies up to 7.2 mm at 100 MeV due to energy degradation. Hyperion applies a spot weight regularisation scheme during IMPT optimisation to reduce the irregularity of individual beam doses.

All plans consisted of three fields delivering 66 Gy (RBE)/33 F homogenously to the PTV (95–107%). All fields were coplanar and the minimum beam separation was 30°. To increase plan robustness with respect to spinal cord dose, field directions were chosen to prevent distal fall off in front of the spinal cord. Additional criteria were used when possible such as avoidance of beams tangentially to the mediastinum, avoiding beams through tissue with a potential risk of large density changes, minimising the distance from beam entrance to tumour, avoiding beam passage through heart.

Dose–volume histograms for IMRT and IMPT plans were compared for iCTV, OARs (heart, lung and oesophagus), and the 95% conformity index CI, given as the volume receiving 95% of the prescribed dose divided by the PTV. Selected dosimetric parameters were compared using a Wilcoxon signed rank test. P-values < 0.05 were considered significant.

Impact of anatomical changes

The impact of the anatomical changes occurring during the treatment course was investigated by recalculation of the IMRT and IMPT plans on two surveillance 4D-CT (sCT) scans acquired approximately at F = 10 and F = 20 for all patients. Re-delineation of target and OARs was performed by a radiation oncologist specialised in lung cancer on all surveillance scans [30]. The dose to OARs was compared between the pCT and the sCTs for photons and protons. To evaluate the impact on the target coverage for IMRT and IMPT, respectively, the iCTV volume receiving 95% of the prescribed dose (V95%) was analysed. Any under-dosage seen was correlated to the anatomical changes observed on the sCT. Proton treatment plans were scaled to prescribed doses of 70, 74 or 78 Gy, to investigate if full iCTV coverage at 95% of 66 Gy = 62.7 Gy could be maintained by increasing the prescribed dose.

Results

Comparison of initial treatment plans

The PTV was covered with 95% dose for at least 99% of the volume for both modalities. Additionally, hot spots above 107% were seen in less than 20 cm^3 for photons and 0.4 cm^3 for protons. The dose to OARs was reduced for the proton plans compared to the photon plans, as exemplified in Fig. 1. Table 1 summarises selected dosimetric parameters for the 23 patients. The median dose to lungs, heart and oesophagus was significantly lower with protons. For lungs and heart, both V20 Gy and V50 Gy were significantly lower for the proton plans. V35 Gy and V50 Gy to the oesophagus were, however not statistically significant. The conformity index was significantly lower for the proton plans.

Impact of anatomical changes, target coverage

Fig. 2 depicts dose distributions for a proton and a photon plan. An atelectasis present on the pCT has disappeared at the sCT at F = 20 resulting in reduced coverage of the iCTV to 65% for the pro-