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

Lone Hoffmann a,⁎, Markus Alber b, Maria Fuglsang Jensen c, Marianne Ingerslev Holt c, Ditte Sloth Møller a

a Department of Medical Physics, Aarhus University Hospital, Denmark; b Department of Radiation Oncology, Heidelberg University Hospital, Germany; and c Department of Oncology, Aarhus University Hospital, Denmark

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a Department of Medical Physics, Aarhus University Hospital, Denmark; b Department of Radiation Oncology, Heidelberg University Hospital, Germany; and c Department of Oncology, Aarhus University Hospital, Denmark

A B S T R A C T

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.

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High rates of local recurrence and toxicity are still predominant in patients with locally advanced non-small cell lung cancer (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.

⁎ Corresponding author at: Aarhus University Hospital, Department of Medical Physics, Norrebrogade 44, Building 5j, 2. Floor, 8000 Aarhus C, Denmark.
E-mail address: Lone.Hoffmann@aarhus.rm.dk (L. Hoffmann).

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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 IIIB (3 patients), IIIA (10 patients), IIIB (6 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 iTV-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 (\(\Sigma\)) and random errors (\(\sigma\)) 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 iTV-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 AQA 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\(^3\) (\(D_{xcm^3}\)) were applied to the lungs (\(V_{20Gy} < 35\%\), mean < 19 Gy), heart (\(V_{50Gy} < 20\%\)), oesophagus (\(D_{\text{mean}} < 66\) Gy) and spinal cord (\(D_{0.05cm^3} < 45\) 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-voxel decomposition which performs well in heterogeneous media [34]. Proton spot beams were aligned on a rectangular scanning grid with 3 x 3 mm scanning pattern and 2 MeV energy layer spacing. The spot size (\(\omega\)) in air at the isocentre was 4 mm. The spot size (\(\omega\)) 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 iTV, 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 iTV volume receiving 95% of the prescribed dose (\(V_{95}\%\)) 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 iTV 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 iTV to 65% for the pro-
ton plan and 95% for the photon plan. The iCTV coverage is shown in Fig. 3.

For all patients, the volume of iCTV covered by 95% of the prescribed dose was compared between pCT and the two sCT scans (see Fig. 4). For photons, six plans were adapted during the treatment course based on the decision support protocol to ensure 99% coverage of the iCTV. Twenty-one patients needed adaptation applying the same criteria to protons at the time of sCT. Alternatively, no patient in the photon cohort needed adaptation compared to 14 (61%) patients in the proton cohort, applying a criterion of only 95% coverage of the iCTV. Of these 14 patients, 13 would require adaptation at fractions 10 and 20, respectively.

The decision support protocol based on geometric deviations observed on daily CBCT developed for photons [18] was used to separate the patients into two groups: A) patients treated with adaptive re-planning during treatment (patients no. 18-23), and B) the remainder of the patients.

For half of the patients in group A (N = 3), atelectasis was resolving. In the remaining three patients, deviations larger than 2 mm and 5 mm for tumour and lymph nodes, respectively, were found. For the photon plans, all these patients showed iCTV coverage <99% [95–99%] in at least one of the sCTs. For the proton plans, the iCTV coverage decreased to median 76% [48–86%] on the sCTs, showing that all patients identified by the geometric criteria designed for photons also require adaptation with protons.

For the 17 patients in group B, deviations in iCTV coverage were less than 1% on sCT for photons. For the proton plans, this

Table 1
Dose to OARs for photon and proton therapy.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Proton, median (range)</th>
<th>Photon median (range)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean lung dose (MLD) (Gy)</td>
<td>6.6 (1.4–12.7)</td>
<td>12.3 (3.3–18.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung V20 Gy (cm³)</td>
<td>11.8 (2.6–21.9)</td>
<td>19.7 (4.6–34.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung V50 Gy (cm³)</td>
<td>5.7 (0.8–12.3)</td>
<td>7.6 (0.8–15.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean heart dose (MHD) (Gy)</td>
<td>1.5 (0.0–5.4)</td>
<td>4.7 (0.4–22.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart V20 Gy (cm³)</td>
<td>2.0 (0.0–8.5)</td>
<td>7.0 (0.0–38.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart V50 Gy (cm³)</td>
<td>0.8 (0.0–5.8)</td>
<td>0.9 (0.0–13.2)</td>
<td>0.011</td>
</tr>
<tr>
<td>Mean oesophagus dose (MOed) (Gy)</td>
<td>15.9 (0.0–33.4)</td>
<td>18.4 (1.5–31.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oesophagus V35 Gy (cm³)</td>
<td>20.4 (0.0–50.1)</td>
<td>23.9 (0.0–47.2)</td>
<td>0.131</td>
</tr>
<tr>
<td>Oesophagus V50 Gy (cm³)</td>
<td>16.2 (0.0–42.8)</td>
<td>18.4 (0.0–39.8)</td>
<td>0.809</td>
</tr>
<tr>
<td>Conformity index (V95%)</td>
<td>1.2 (1.1–1.4)</td>
<td>1.3 (1.1–1.5)</td>
<td>0.0085</td>
</tr>
</tbody>
</table>
decreased to a median of 97% (range: 60–100%). Under-dosage exceeding 5% of the iCTV was seen for eight patients. These deviations derive from daily variations in patient positioning resulting in non-rigid changes in the position of bones. Shifts of 5–15 mm were seen for the shoulder (6 patients) and ribs (5 patients). In addition, changes up to 10 mm in the position of the diaphragm were seen in one patient with a tumour close to the diaphragm.

For all patients in group B, the iCTV would receive 95% of 66 Gy (see Table 2) when prescribing 74 Gy. For patients in group A, the benefit of increasing the dose was limited. Only two patients would be treated sufficiently with a 78 Gy prescription. When the prescribed dose is increased, the median MLD, MHD and MOeD are still lower than those obtained for photons (see Tables 1 and 2). The maximum dose to the 1 cm$^3$ of the oesophagus, trachea, bronchi, and heart increases and may thus be the dose limiting factor.

Impact of anatomical changes, OAR

For the OARs, changes in dose on both sCTs were investigated. The dose to the spinal cord remained below 45 Gy for all patients. The median change in MLD on the sCTs was 0.1 Gy [−2.4 to +3.4 Gy] and 0.1 Gy [−1.3 to +1.0] for the proton and photon plans, respectively. For the oesophagus, an increase in $D_{1cm^3}$ exceeding the prescribed (dose of) 66 Gy was seen in 12 patients (proton plans) with a median dose increase of 2 Gy and maximum 6 Gy. For the photon plans, $D_{1cm^3}$ increased less than 2 Gy.

Discussion

In a comparison between IMRT and IMPT plans for 23 patients we showed a significant reduction in dose to OARs. Only the 1 cm$^3$-volume receiving high doses in the oesophagus had no difference between the two modalities. This is probably due to the oesophagus being often adjacent to mediastinal lymph nodes. The reduction in dose to OARs is in agreement with the findings of other studies [4,6,7].

A decision support protocol based on geometrical measures of target positioning and large anatomical changes such as appearance of an atelectasis or pleural effusion, implemented clinically for RT [18], was tested for PT. The protocol correctly identified patients with large target under-dosage (group A). The protocol is based on geometric evaluations of daily CBCT images and prescribes re-planning for systematic deviations. Additionally, target under-dosage was observed for a group of patients with non-rigid changes in the positioning of the bones (group B). These deviations could be included in the protocol by evaluating systematic deviations larger than 5 mm on the vertebra, shoulder and ribs. No under-dosage was seen when using photons.

In conclusion, 61% of the patients would require adaptation of their proton plan with a 95% coverage of iCTV. This is a higher adaptation frequency than seen in studies of lung cancer patients with passively scattered PT [8,22–23] underlining that IMPT for lung cancer patients requires a large number of adaptations. Differ-
ent criteria for re-planning are used in clinical and planning studies. Furthermore, the clinical evidence for the target coverage required is limited. We have shown a significant decrease in the local recurrence using ART [19]. In the former study, the limit for adaptation was set to a decrease of 1% in the coverage of the iCTV. However, the study was based on a small cohort of 104 patients and evidence from larger cohorts is required. The frequency of adaptations is highly dependent on the limits for target coverage and the constraints for OARs. We found that high doses to the oesophagus may occur during treatment and dose to the oesophagus should be a criterion for adaptation of the proton plans. The dose to the spinal cord remained below the constraints in all patients. The frequency of adaptations due to risk of overdosing OARs will depend on beam angles. In the present study, the beams were chosen not to stop in front of the spinal cord and if possible not in front of other OARs.

In the current study, a PTV was used to secure coverage of the iCTV. The PTV concept is debatable in proton therapy and the photon margins cannot be transferred directly to PT, but was used here for comparison. If PTV margins are used for clinical proton plans, the margins should rely on machine and centre specific numbers. An alternative to the PTV-margin is robust optimisation. This has been shown to reduce the high frequency of adaptations in planning studies [5,24,35–36]. Robust optimisation includes user-defined rigid geometric shifts in the optimisation process, whereby the treatment plan becomes robust against minor rigid shifts in set-up position. However, the perturbation of the delivered dose derives from many different sources. Large anatomical changes such as the appearance of an atelectasis cannot be included in robust optimisation. This can, however, be identified by a decision support protocol. Non-rigid changes in position of the diaphragm or the bones (e.g. the shoulder blades or ribs) have an impact on the PT dose distribution, while the photon counterpart is nearly unaffected. Dose deviations due to these changes are seen in 35% of the patients, and while small rigid set-up errors can be included in robust optimisation [5,24,35–36], the question regarding correction of larger non-rigid errors remains unanswered. The largest obstacle to scenario-based robust optimisation is prediction of the non-rigid geometrical changes that might occur. We found that positional changes up to 15 mm were seen for shoulder blades and ribs. In a planning study of Szeto et al. [25] using robust optimisation, eight out of sixteen patients needed plan adaptations during the treatment course. Atelectasis, tumour deformation/growth, and changes in bone positioning were found to cause target under-dosage [25]. Here, we confirm that adaptation is much more crucial for PT than for photon therapy. However, the decision to adapt the treatment plan should be based on systematic anatomical changes as day to day changes require daily replanning.

Intra-fractional breathing motion and interplay effects were not considered in the current study, effectively simulating a gated treatment. Treatment plans were based on iCTV delineations using the mid-ventilation phase of a 4DCT scan. The evaluation of the inter-fractional changes was based on re-delineation of the target at similarly acquired 4D CT surveillance scans, hereby minimising the effect of the intra-fractional motion. The dose deviations arising from breathing motion has been shown to be much smaller than the inter-fractional deviations studied here [25,37].

The target under-dosage may be compensated by a higher dose prescription and a required 95% coverage of the iCTV by 66 Gy during the full treatment course. The under-dosage due to non-rigid positioning errors disappeared when the prescribed dose was increased to 74 Gy. In contrast, the majority of patients with large anatomical changes in this study needed adaptation of the proton plan during treatment regardless of an increase in prescribed dose to 78 Gy. The combination of an increased prescription dose and incorporation of the adaptive protocol for PT would indeed ensure target coverage for all patients. However, this introduces a higher risk of over dosage of OARs which may depend on the margins used and may call for a more heterogeneous dose prescription.

In conclusion, a significant reduction in dose to OARs can be obtained for IMPT compared to IMRT, but requires a high proportion of adaptations. Large anatomical changes can be corrected for by an adaptive protocol such as the one used for photons. Non-rigid positioning errors are not identified by the geometrical criteria used for photons, and are not currently implemented in the robust optimisation algorithms. These can, however, be compensated by an increase in the prescribed dose keeping in mind that this requires additional attention to OARs. Daily imaging and frequent treatment adaptation for a high fraction of patients is mandatory in proton therapy for loco-regional lung cancer.

**Conflict of interest statement**

None.

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Adaptive proton therapy for lung cancer


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