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Original article

Treating locally advanced lung cancer with a 1.5 T MR-Linac – Effects of the magnetic field and irradiation geometry on conventionally fractionated and isotoxic dose-escalated radiotherapy

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ABSTRACT

Purpose: This study investigates the feasibility and potential benefits of radiotherapy with a 1.5 T MR-Linac for locally advanced non-small cell lung cancer (LA NSCLC) patients.

Material and methods: Ten patients with LA NSCLC were retrospectively re-planned six times: three treatment plans were created according to a protocol for conventionally fractionated radiotherapy and three treatment plans following guidelines for isotoxic target dose escalation. In each case, two plans were designed for the MR-Linac, either with standard (~7 mm) or reduced (~3 mm) planning target volume (PTV) margins, while one conventional linac plan was created with standard margins. Treatment plan quality was evaluated using dose–volume metrics or by quantifying dose escalation potential.

Results: All generated treatment plans fulfilled their respective planning constraints. For conventionally fractionated treatments, MR-Linac plans with standard margins had slightly increased skin dose when compared to conventional linac plans. Using reduced margins alleviated this issue and decreased exposure of several other organs-at-risk (OAR). Reduced margins also enabled increased isotoxic target dose escalation.

Conclusion: It is feasible to generate treatment plans for LA NSCLC patients on a 1.5 T MR-Linac. Margin reduction, facilitated by an envisioned MRI-guided workflow, enables increased OAR sparing and isotoxic target dose escalation for the respective treatment approaches.

Current survival rates for patients with locally advanced non-small cell lung cancer (LA NSCLC) are poor [1,2]. In spite of improvements in both radiotherapy technology and systemic therapies, some suggest that current treatment strategies have reached their therapeutic ceiling [3]. Effective local disease control is essential for the survival of these patients [1]. Taking heed from stereotactic radiotherapy for early-stage NSCLC patients, where biologically equivalent doses of 100 Gy and more result in local disease control rates greater than 90% [4], dose intensification continues to be investigated in LA NSCLC patients. Indiscriminate target dose escalation, delivered with a prolonged overall treatment course, may be detrimental [5,6]. However, data have shown promising outcomes in LA NSCLC patients treated with accelerated isotoxic dose-escalated radiotherapy [7–11], where each patient was prescribed an individualized target dose, escalated on the basis of normal-tissue tolerances up to a trial-specific maximum target dose [3].

During a course of radical radiotherapy for LA NSCLC patients, there can be substantial inter- and intra-fractional changes in thoracic anatomy, due to respiratory and cardiac motion, patient weight loss, tumour growth or shrinkage, or changes in the surrounding lung [12,13]. Daily cone-beam CT scans are utilized to set patients up according to the observed tumour position and any remaining uncertainties are accounted for using planning target volume (PTV) margins. However, large margins result in increased irradiation of healthy tissue and restrict isotoxic target dose escalation.

Recently, MRI-guided treatment units have emerged, allowing acquisition of MR images immediately prior to and during

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radiotherapy delivery [14–17]. The availability of these images with improved soft-tissue contrast may increase target delineation reproducibility, as has been shown for other tumour sites, and reduce setup uncertainties [18–20]. Integrating MRI-guided units into clinical practice has implications for treatment planning as treatments will be delivered within a static magnetic field. These differ from the ones delivered at zero magnetic field because the trajectories of secondary electrons are altered by the Lorentz force [21,22] and may cause local increases in dose ("hot spots"), especially at air-tissue-interfaces, where electrons can loop around and deposit energy at the surface they have been ejected from [23]. Furthermore, the irradiation geometry and beam energy of MRI-guided units deviate from the ones realized for conventional linacs.

Several studies have evaluated the effect of magnetic fields and irradiation geometry on stereotactic radiotherapy of early-stage NSCLC [24–29]. However, none have specifically investigated the use of MRI-guided units for treatment of patients with LA NSCLC. This study used an isotoxic dose-escalated trial protocol as well as a conventionally fractionated scheme to generate treatment plans for a conventional linac and plans for a 1.5 T MR-Linac using standard or reduced margins. By comparing the planned dose distributions we explored the hypothesis that it is feasible to create clinically acceptable radiotherapy plans for the MR-Linac. Furthermore, the effect of reducing PTV margins with regard to sparing of healthy tissue and potential target dose escalation was investigated.

Material and methods

Patient datasets and contouring

For this study we used treatment planning 4DCT scans of ten consecutive patients undergoing radical radiotherapy for LA NSCLC at our institution. The scans were acquired using a Philips Brilliance CT Big Bore scanner (Philips Medical Systems, Best, the Netherlands) with a voxel size of $\sim 1 \times 1 \times 2\ mm^3$. Details of the patient characteristics can be found in the Supplemental material. All patients had given written, informed consent for their scans to be used for research purposes.

One clinician contoured the gross tumour volume (GTV) on each of the ten phases of the 4DCT scan. In order to account for microscopic disease spread, each GTV contour was expanded isotropically by 5 mm to derive the clinical target volumes (CTV). Afterwards, the union of the CTV contours was used to create the internal target volume (ITV) on the average CT image, which was derived from the 4D acquisition.

Two different margin approaches were used to calculate the planning target volume (PTV). Standard PTV margins expanded the ITV by approximately 7 mm, depending on direction, and emulate the clinical standard at our institution. A smaller PTV using reduced margins of approximately 3 mm was also created. This was motivated by the potential reduction of treatment uncertainties with the envisioned MR-Linac workflow that would incorporate patient imaging, delineation of critical structures and adaptation of the treatment plan before each fraction [30]. We assume that the use of MR images with high soft-tissue contrast allows for more accurate target delineation and localization. Additionally, a future MR-Linac workflow could potentially incorporate plan re-optimization for each fraction and allow adaptation of the ITV to inter-fractional changes in tumour motion magnitude. Both PTV margins were calculated using van Herk's margin recipe and Table 1 summarizes the individual error contributions, which were either derived from clinical judgment or taken from the literature [31,32]. While this approach disregards the contouring accuracy on MR images depending on the position of the tumour relative to other soft tissues, a revision of the margin concept is beyond the scope of this study.

The mediastinal envelope, heart, oesophagus, brachial plexus, spinal canal, skin and lungs were delineated on the average CT image. The lung structure was defined as both lungs minus the union of all GTV contours. The skin was defined as the 5 mm rind of the patient contour.

Treatment planning technique and machine models

All treatment plans were designed using the Monaco treatment planning system (Elekta AB, Stockholm, Sweden), research version 5.19.02. Monaco allows for treatment plan optimization and dose calculation under consideration of the magnetic field. Its dose calculation also accounts for the irradiation geometry of the prototype of the 1.5 T MR-Linac, such as the specific beam energy, beam filtration, fixed isocenter, source-to-axis distance and the MLC leaf width at isocenter. Key differences to the conventional Elekta Versa HD linac are provided in Table 2.

For each patient case, we designed treatment plans following two different protocols. One set of plans was designed according to a conventional fractionation protocol with 55 Gy in 20 fractions. The other plans were created based on the United Kingdom isotoxic intensity modulated radiotherapy (IMRT) trial protocol that allows for isotoxic target dose escalation up to 79.2 Gy in 44 fractions (treating twice daily) by increasing the number of 1.8 Gy fractions until an organ-at-risk (OAR) constraint is reached [33]. For this study, we adapted the protocol and removed the artificial limit on maximum target prescription dose. Planning guidelines for both protocols can be found in the Supplemental material. For each of the two planning approaches, three plans were generated: one for the conventional Versa HD linac without a beam flattening filter and two for the MR-Linac. Treatment plans for the MR-Linac were designed with either standard or reduced PTV margins, whereas plans for the conventional linac were generated using standard PTV margins.

All plans were generated using step-and-shoot IMRT with nine equidistant, coplanar beams. The beam isocenter was positioned at the centre of the ITV for the conventional linac treatment plans and fixed at the centre of the MR bore, 13 cm above the treatment couch's surface for the MR-Linac plans. In order to ensure comparability of all plans, the plans were scaled so that the mean ITV dose was equal to the respective prescription level. Additionally, we used similar optimization functions and equal plan modulation options for all treatment plans per respective treatment protocol. All dose distributions were calculated as dose-to-medium dose using Elekta's Monte Carlo engine based on work by Hissoiny et al. [34] with a statistical dose uncertainty of 2% per calculation on a dose grid of $0.25 \times 0.25 \times 0.25\ cm^3$.

Plan evaluation

For each patient, the dose to OAR and potential for target dose escalation calculated for the conventional linac was compared to that for the MR-Linac with standard margins to investigate the effect of the different irradiation geometries. Similarly, plans for the conventional linac were compared to those for the MR-Linac with reduced margins to assess the effect of additional margin reduction.

Conventionally fractionated plans were compared by evaluating differences in several dose–volume metrics. Statistical significance of the differences was evaluated with a paired *t*-test after confirming normal distribution using Lilliefors test [35]. Five metrics of primary interest were chosen on a *pre-hoc* basis, because they either have been shown to be associated with treatment toxicity, they are highly influential during plan optimization or because of

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