ORIGINAL ARTICLE

A method for selection of beam angles robust to intra-fractional motion in proton therapy of lung cancer

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ABSTRACT

Background. Proton therapy offers the potential for sparing the normal tissue surrounding the target. However, due to well-defined proton ranges around the Bragg peak, dose deposition is more sensitive to changes in the water equivalent path length (WEPL) than with photons. In this study, we assess WEPL variations caused by breathing-induced motion for all possible beam angles in a series of lung cancer patients. By studying the association between measures for WEPL variation and breathing-induced target dose degradation we aimed to develop and explore a tool to identify beam angles that are robust to patient-specific patterns of intra-fractional motion.

Material and methods. Using four-dimensional computed tomography (4DCT) images of three lung cancer patients we evaluated the impact of the WEPL changes on target dose coverage for a series of coplanar single-beam plans. The plans were optimised for the internal target volume (ITV) at the maximum intensity projection (MIP) CT for every 3° gantry interval. The plans were transferred to the ten 4DCT phases and the average reduction in ITV V95 over the ten phases, relative to the original MIP CT calculation, was quantified. The target dose reduction was associated with the mean difference between the WEPL and the phase-averaged WEPL computed for all beam rays across all possible gantry-couch angle combinations.

Results. The gantry-couch angle maps showed areas of both high and low WEPL variation, with overall quite similar patterns yet with individual differences reflecting differences in tumour position and breathing-induced motion. The coplanar plans showed a strong association between WEPL changes and ITV V95 reduction, with a correlation coefficient ranging between 0.92 and 0.98 for the three patients (p < 0.01).

Conclusion. We have presented a 4DCT-based method to quantify WEPL changes during the breathing cycle. The method identified proton field gantry-couch angle combinations that were either sensitive or robust to WEPL changes. WEPL variations along the beam path were associated with target under-dosage.

Lung cancer is the third most frequent cancer disease, following breast and prostate, and it has the highest mortality rate of all cancer diseases [1–3]. During recent years a number of treatment approaches, including different radiotherapy (RT) techniques and drugs, have been developed and applied for several stages of the disease [4], with the aim of reducing lethality and morbidity rates.

In the management of in particular non-small cell lung cancer (NSCLC), RT is usually given as intensity-modulated RT (IMRT) or stereotactic body RT (SBRT). Some studies are indicating better dose coverage for SBRT at early stage of NSCLC and lower morbidity rates for proton therapy for stage III disease [5–8]. The interest in the use of proton therapy is increasing since, theoretically, the favourable depth dose characteristics of proton beams can allow for a better sparing of normal tissue than what can be achieved with photons. However, due to the finite range of protons in the tissue, protons are more sensitive to motion and anatomy changes than photons [9–11].
For tumours in the thorax, such as lung tumours, it is in general important to account for the intra-fractional motion induced by patient respiration, as well as the inter-fractional motion and other anatomy changes, such as tumour shrinkage and weight loss occurring on a longer time scale (days to weeks). These factors have been studied and quantified by several groups using different techniques [12–16]. For particle and proton therapy, organ motion in the target area and in the beam path can change the radiological path length and, as a result, the dose distribution delivered to the tumour and the normal tissues [17–19]. Much research has focused on so-called interplay effects, i.e. redistribution of dose when the tumour moves with respect to the dynamic beam [20]. The aim of these studies has been to account for the uncertainties in the RT planning and delivery process in order to optimise margins and hence tumour coverage as well as to spare more normal tissues [21–26].

In order to mitigate the dosimetric degradation due to anatomical changes, several groups have evaluated different margin configurations and treatment techniques for lung tumours. Chang et al. [12] compared several RT delivery techniques (including both photons and protons) as well as different adaptations to motion and inter-fractional changes. Wang et al. [23] evaluated different strategies for lung proton planning based on 4DCT scans, including maximum intensity projections (MIP), average intensity projections and peak exhale images. Knopf et al. [24] studied a number of margin configurations for spot-scanning proton therapy based on the organ motion changes and related WEPL changes. Very recently, Mori et al. [25] studied variation due to both intra- and inter-fractional changes in the anterior-posterior beam eye’s view WEPL, considering dose variations for anterior-posterior beam configurations due to chest wall thickness modifications. Interplay effects due to breathing movement (that leads to density changes in the ray paths) may considerably influence RT of lung cancer. In particular, when considering protons for lung tumours, plan techniques should take into account changes in the WEPL, both intra- and inter-fractional.

When treating with protons, usually a lower number of beam angles are used compared to treatment with photons. Beam angle selection is therefore important for an optimal result of the dose deposition, since anatomical changes play an important role. The aim of this study was therefore to develop a method that can be used to assist beam angle selection for proton therapy of lung cancer. In this study we developed a metric to assess the changes in the WEPL for all possible gantry-couch angle throughout the breathing cycle. The metric was correlated with target dose degradation due to breathing, providing a tool to select the most consistent and robust treatment geometries.

**Material and methods**

Image data sets from three patients in the open source data set of the POPI project (http://www.creatis.insa-lyon.fr/rio/popi-model) were used in this study. Each patient had a 4DCT scan with ten phases as well as MIP and average position projection image sets; further details of the image acquisitions and the available data are described in detail by Vandemeulebroucke et al. [27]. The three selected patients all had a right-sided lung tumour, in order to explore the method in a homogeneous group of patients (Supplementary Figure 1, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.927586).

For each patient, the clinical target volume (CTV) was initially outlined in all ten phases, followed by the creation of the internal target volume (ITV) as the union of all outlined CTVs. The structures were outlined using the Eclipse v.11 treatment planning system (TPS) (Varian Medical Systems, Palo Alto, CA, USA) and exported as structure files.

To evaluate the dose coverage we created for each patient 61 single-beam spot scanning proton plans using the TPS TRig v.1001c [28–30]. The plans covered beams for every 3° gantry angle in the interval from 180° to 360°, all with a 0° couch angle, avoiding radiation through the contralateral lung (all patients had right-sided tumours). The proton pencil beams had a 5 mm full width at half maximum spot size and a 2 mm spot space. Each plan was created and optimised based on the MIP image set and on the ITV structure, and were all normalised to obtain $V_{95} = 95\%$ of the ITV for each plan, i.e. 95% of the volume received 95% of the prescribed dose.

To assess changes in the target dose coverage due to the breathing movement we transferred each single-beam plan to the ten 4DCT phases to obtain dose-volume histograms (DVH) for each phase at each CTV. The DVHs of the CTVs were averaged over all ten phases creating an average DVH for the CTV, which was compared with the reference DVH obtained at the MIP image set. The metrics used to compare CTV dose coverage for each angle included the difference in the $V_{95}$ between the optimised plan and the plan recalculated in the ten 4DCT phases, referred to as the CTV $V_{95}$ reduction. All evaluated dose endpoints were physical dose.

To evaluate the changes in the WEPL over the breathing cycle and for all beam angle configuration we developed an in-house PyTRig [31] algorithm based on Python v.2.7.5 and Matlab 2011 (The MathWorks, Natick, MA, USA). The WEPL values were extracted from the CT images applying a con-
version table from Krämer et al. [29] (note that these tables are not universal and should be adapted for each clinical facility). The following points describe the steps of the workflow for each beam angle configuration (see also Supplementary Figure 2, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.927586):

1. A plane crossing the isocenter and perpendicular to the beam, called the isocenter plane, was defined.
2. All rays hitting the ITV structure were selected.
3. For the MIP image set and for the ten 4DCT phase image sets, the beams eye view WEPL map (BEV map) was calculated; the BEV map is a 2D map at the isocenter plane, where each voxel represents the sum of all the voxels along the ray path from the source to the isocenter plane (Supplementary Figure 2A available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.927586).
4. The absolute value of the difference between the BEV maps of each 4DCT phase and the MIP image was calculated.
5. The differences of the BEV maps were averaged over all the ten phases, obtaining a 2D map (ΔWEPL BEV map), where each voxel stored the average difference between MIP WEPL and the phase WEPLs, for each ray (Supplementary Figure 2B available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.927586).
6. The ΔWEPL BEV map was averaged over all considered ray paths to extract a unique value for each beam angle.

The mean ΔWEPL value was calculated for all gantry-couch angle combinations and represented in a 2D map (mean ΔWEPL map). The calculations were performed for every gantry angle from 0° to 360° with a 3° interval, and for couch angles from −90° to 90° also in a 3° interval. Finally, the associations between the WEPL change metrics and the CTVV95 reductions were analysed, quantified using the linear Pearson’s correlation coefficient.

Results
The reference DVHs of the MIP image for the 61 single-beam plans were compared to the average DVHs across the ten 4DCT phases (Figure 1). For the case shown in Figure 1 (Patient 1), as well as for Patient 2 (Supplementary Figure 3A, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.927586), the MIP optimised plans had better target volume coverage than the averaged DVHs at all analysed beam directions, i.e. the plan re-calculated over all ten phases indicated an under-dosage for all gantry positions. For patient 3 (Supplementary Figure 3B available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.927586) we found both angles with an increase and angles with a decrease in target coverage when comparing the optimised plan with the corresponding average dose distribution along the breathing cycle. The CTVV95 reductions for the three patients are shown in Figure 2.

The mean ΔWEPL map for the three patients across the gantry-couch angles showed similar patterns, identifying areas of both high and low variation (Figure 3). However, there were differences in the
obtained values for specific beam angles. For a 0° couch angle, the mean $\Delta$WEPL profiles values varied three to six-fold over the gantry angles, with a coefficient of variation ranging from 42% to 54% across the patients (Figure 4).

The mean $\Delta$WEPL was found to have a strong correlation with the CTV $V_{95}$ reduction (Figure 5), with Pearson’s correlation coefficients of 0.98, 0.92, 0.96 for patients 1, 2 and 3, respectively ($p < 0.01$).

**Discussion**

In this study, we have presented and initially explored a method to evaluate the robustness of all possible proton beam gantry-couch angles for proton therapy of lung cancer, considering the dose degradation due to breathing-induced changes in the WEPL. In the three cases investigated, the suggested measure was found to have a strong correlation with the dose degradation found across all investigated beam angles.

The mean $\Delta$WEPL maps for the three patients showed overall the same patterns, much due to a similar tumour location for all three cases. However, the mean $\Delta$WEPL also reflects particular features of each patient’s breathing cycle and anatomical features, as can be seen with the different values among patients for the same specific gantry-couch angle combination. Considering the results in Figure 4, the aforementioned minimum in the profile is due to similar patterns of tumour movement, where its prevailing motion directions are anterior-posterior and cranio-caudal. For lateral beam angles, there is less

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**Figure 3.** 2D maps for the three patients showing the mean value of the differences between the MIP (reference) WEPL and the average WEPL of all the phases. Non-deliverable angle combinations have been cropped. All three patients had a tumour in the central right lung; patients 1 and 2 both had an isolated tumour, whereas the tumour of patient 3 was connected to the posterior part of the chest wall.

**Figure 4.** Changes in the WEPL for patients 1 to 3 for the 61 single-beam configurations (the average of the $\Delta$WEPL). This metric takes into account the changes in the WEPL between the reference image (used to optimise the plans) and the phases over all the breathing cycle.

**Figure 5.** Scatter plot for patients 1 to 3 showing the strong association for each patient between the $V_{95}$ reduction with the mean $\Delta$WEPL. The values for the linear correlation coefficients are 0.98, 0.92 and 0.96 for patients 1, 2 and 3, respectively ($p < 0.01$).
variation along the beam direction, and differences between patients correspond to anatomical changes and movements in the structures surrounding the tumour. This reasoning could be applied to rays going through the opposite lung, where the mean $\Delta$WEPL has large values (Figure 3), because the proton paths go through larger distances in the body, and therefore are more affected by anatomical changes. The mean $\Delta$WEPL had a minimum between gantry angles of $240^\circ$–$270^\circ$ (Figure 5). These minima in mean $\Delta$WEPL may be a result of the absence of high WEPL structures moving in or out of the beam during the breathing cycle, like ribs.

Although a limited number of patients have been investigated in this first exploration of the proposed metric, our results suggest that the metric quantifying WEPL changes is highly correlated with dose coverage variation, with a Pearson’s coefficient ranging between 0.92 and 0.98. We also explored other metrics to take into account the WEPL changes, like the WEPL standard deviation over the ray paths, including combinations between $\Delta$WEPL standard deviation and $\Delta$WEPL mean value. Finally, we found that the mean $\Delta$WEPL follows the under-dosage metrics, and are reasonably consistent within the three analysed patients. In particular, for the presented WEPL change metric, the absolute difference between related ray paths at the reference and moving image set were quantified. Then, the WEPL difference was averaged over all the ray paths and related with dose changes extracted from the DVHs. Both dose changes and WEPL changes correspond to averaged values of dose volumes and WEPL, respectively, which might have improved the correlation between the two metrics. Anyhow, the metric should be tested in a larger cohort of patients in order to clarify its general applicability.

In this study, we have used the ITV as target volume, created as the union of all the CTVs in the different breathing phases. Despite the recommendation from Knopf et al. [24], to assess exclusively the WEPL change metric and its relation with the dose coverage, neither margins nor range adaptations were implemented. It is well known, and reported by several authors [12,23], that plans optimised in the MIP generates larger high-dose volumes, and normally these volumes are shifted distally. This happens because in the MIP image higher values of WEPL are artificially introduced. In this study, due to particular features of the used TPS (i.e. features of dose optimisation in steep density gradients volumes), dose calculations were done in the MIP. Otherwise optimisations where air volumes surroundings were involved yield unrealistic results for the fluence maps, causing poor dose distributions inside the ITV. However, the method to obtain the relation between the changes in the WEPL and dose degradation can be implemented and fit to the particular features of the TPS, or to other image set optimisation such as the average image set or the breathing cycle reference image set.

Compared to previous studies [17,25] the present paper provides a method where all beam angles are evaluated and compared. The method identifies to which degree different beam paths will be influenced by WEPL changes due to the respiratory cycle. In terms of calculation times, the method is quick and should therefore be feasible for implementation in the clinical workflow to guide proton treatment plan design. For example, a complete 2D map evaluating all possible beam angles would take around five minutes on a commodity computer. In fact, the next step will be to explore the metric in a larger and more heterogeneous cohort of patients, and evaluate its suitability to incorporate the method into the clinical workflow.

For treatment planning one would be interested in the best, i.e. most robust angles; instead of calculating a full couch/gantry map the algorithm can return the best angles (e.g. the five most robust angles), e.g. with a $10^\circ$ spacing; such a calculation can be done within a minute. Also, the mean $\Delta$WEPL measure could be used as a penalty factor if incorporated into the intensity-modulated proton therapy optimisation algorithms. Further in this direction of beam angle selection, it would be of interest to also take the normal tissue doses and the ‘robustness’ of these into account. Besides, the method could be extended to generate directional margins, related to each specific patient anatomy and respiratory movement. Finally, this approach could also be a tool to evaluate both inter- and intra-fractional WEPL changes and their related degradation of target dose coverage.

In conclusion, in this study we have presented a method to evaluate changes in the WEPL during the breathing cycle using 4DCT images. By studying the associations between the WEPL variations and degradations of target dose coverage, the method could successfully identify proton field gantry-couch angle combinations that were either sensitive or robust to WEPL changes in the three patients analysed. Following further investigation in a larger patient cohort, the method could become a useful tool for selection of robust beam angles in proton therapy of lung cancer.

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