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Proton pencil beam scanning treatment of free-breathing lung cancer patients – is 5 mm motion a limit?

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Background

The interplay effect might degrade the dose of pencil beam scanning proton therapy to a degree that free-breathing treatment might be impossible without further motion mitigation techniques, which complicate and prolong the treatment. We assessed whether treatment of free-breathing patients without motion mitigation is feasible.

Material/Methods

For 40 lung cancer patients, 4DCT datasets and individual breathing patterns were used to simulate 4D dynamic dose distributions of 3D treatment plans over 33 fractions delivered with an IBA universal nozzle. Evaluation was done by assessing under- and overdosage in the target structure. The impact of using beam-specific target volumes and the impact of changes in motion and patient anatomy in control 4DCTs were assessed.

Results

Almost half of the patients had tumour motion amplitudes of less than 5mm. Under- and overdosage was significantly smaller for patients with tumour motion below 5mm compared to patients with larger motion (2% versus 13% average absolute reduction of V95, 2% versus 8% average increase in V107, $p<0.01$). Simulating a 33-fraction treatment, the dose degradation was reduced but persisted for patients with tumour motion above 5mm (average ΔV95 of <1% vs 3%, $p<0.01$). Beam-specific target volumes reduced the dose degradation in a fractionated treatment, but were more relevant for large motion. Repeated 4DCT revealed that changes in tumour motion during treatment might result in unexpected large dose degradations which would need to be accounted for by adaptive planning.

Conclusion

Tumour motion amplitude is an indicator of dose degradation caused by the interplay effect. Fractionation reduces the dose degradation allowing the unmitigated treatment of patients with small tumour motions of less than 5mm. The beam-specific target approach improves the dose coverage. The tumour motion and position needs to be assessed during treatment for all patients, to quickly react to possible changes which might require a treatment adaptation.

Keywords: pencil beam scanning, proton therapy, lung cancer, interplay, motion

Introduction

Recently, the Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee published a consensus statement regarding indications of proton therapy (PT) for lung cancer (1). They describe that pencil beam scanning (PBS) PT requires adequate motion management, robustness optimization, and strict quality assurance. The reason for these requirements lay, amongst others, in the inherent difficulty of treating a mobile tumour with a scanned beam application technique which leads to dose distortions by the so-called interplay effect (2). The impact of this effect has been substantially explored in phantom and virtual studies (eg 3–6) leading to the conclusion that motion mitigation in the form of rescanning, gating or tracking, or combinations there-of are mandatory. Furthermore, the effect depends largely on individual machine parameters (eg spot size, spot position change time, spot delivery sequence) as well as patient characteristics (breathing pattern, tumour motion amplitude), and thus is difficult to describe on a generalised basis. Machine- and patient-specific evaluation of the effect for a set of treatment parameters is needed. The clinical implementation proposed by Chang et al for thoracic treatment sites (7) includes a set of criteria from the individual patient data. For example, in order to consider the patient for PBS PT the tumour motion amplitude and the water equivalent thickness change along the beam direction should be less than 5 mm. Furthermore, a robust treatment planning approach should be implemented for multiple-field optimised plans, which is based on in-house software. While robust treatment planning is advised for PBS PT, it is not yet a widespread technique since commercial solutions are only just becoming available in existing treatment planning systems (1). Furthermore, up to now, most of these approaches only consider uncertainties in range and set-up, but not the consequences of motion, such as the interplay effect. This might be insufficient for motion mitigation in PBS PT of lung

cancer. Breath-hold or gating strategies might be an option to reduce motion and could be relevant during treatment (8). However, especially for patients with lesions in the lung, it might be difficult to perform a breath-hold, or even breathe regularly enough for sensible gating. Thus, these approaches have their own disadvantages and might be difficult to implement. The use of rescanning is found to decrease the effect of motion on the dose distribution, but this approach prolongs the treatment time for slow scanning facilities, especially if a large number of rescans is required as might be the case for large tumour motions (9,10).

Thus, we assessed the practicality of using PBS PT in free-breathing patients without the use of any motion mitigation technique, aiming to identify patients for whom this treatment approach can be used. For this purpose, in the presented retrospective analysis the impact of tumour motion assessed with 4DCT imaging on the dose distribution of single-field optimised PBS treatment plans was evaluated for the characteristics of our treatment machine.

Materials and methods

Treatment planning data

4DCT imaging data of 40 consecutive patients receiving photon stereotactic body radiotherapy at our institution between August 2012 and September 2013 were collected including the individual breathing pattern of these patients. All patients gave written consent for the use of their data. The study was approved by the local ethics committee (EK 301082013). 4DCT imaging was done with a Siemens SOMATOM Sensation open CT scanner (Siemens Healthcare, Erlangen, Germany). The 4DCT image stacks consisted of eight reconstructed image series (CT phases), using a local-amplitude-based sorting of the CT raw-data based on the patient‘s breathing pattern. The breathing

patterns were recorded using a pressure belt respiratory gating system (Anzai Medical Co., Ltd, Tokyo, Japan). Image sample period was 500 ms (CT gantry rotation time of 1 s). The CT phases were individually distributed throughout the patient's breathing pattern to get a homogeneous sampling of motion states, but always included maximum inhale and maximum exhale. Gross target volume (GTV) was delineated on all eight CT phases independently and then merged into an internal gross target volume (iGTV). A uniform extension of 4 mm was done to generate a planning target volume (PTV) for each GTV, merging all PTVs to an iPTV as planning target. Tumour motion peak-to-peak amplitudes were identified in cranio-caudal, left-right and anterio-posterior direction based on the centre-of-mass of the delineated eight GTVs. 3D Treatment planning was performed with the in-house software PSIplan at the Paul Scherrer Institute (PSI) in Villigen, Switzerland. The CT dataset for treatment planning was the 15 % inhale phase, which represents an average anatomy of the patient. The Hounsfield Units (HU) in the iGTV were overwritten with a fixed value of 50 similar to the treatment planning approaches presented by Kang et al. and Grassberger et al. (5,11). For all patients, single-field optimisation was chosen, generating treatment plans with three equally weighted beams. Beam directions were chosen individually depending on tumour location in order to reduce the dose exiting into healthy tissue. The dose calculation grid was set to 2x2x2 mm^3. The spot size varied between 3 mm to 8 mm sigma in air depending on the energy and the spot distance was set to 1 sigma between spots. The simulated treatment consisted of 33 fractions with 2 Gy(RBE) per fraction.

4D dynamic dose calculation

The 4D dose calculation was based on an in-house software developed at PSI. Relevant machine parameters for the 4D calculation were adjusted to match the proton gantry from Ion Beam Applications (IBA) with a universal nozzle (energy switching time of

2 s, spot position changing in 1.5 ms, minimum time for any spot irradiation of 2 ms). Anatomical changes due to motion during simulated treatment were taken from the 4DCT image data including voxel position changes and density changes in the beam path. Voxel mapping was done by deformable image registration using a B-Spline algorithm of the software Plastimatch (12). A detailed description of the 4D calculation process can be found in Boye et al. (13). In short terms, each spot is assigned a time stamp depending on its time point in a subsequent delivery depending on the nominal machine parameters (timing to move from spot to spot, duration of spot irradiation, spot sequence) and plan parameters (spot dose, spot positions). This time stamp is then matched to a time stamp map of the breathing pattern of the patient identifying the 4DCT phase in which the patient would be at that time point. The dose for the spot is then adapted according to the changed anatomy in which it would be applied. The sum of all spot doses on the planning CT gives a 4D dynamic dose distribution. Spot sequence started with the highest energy spots, applying all spots of this layer in a meander pattern, than switching to the second-highest energy and so on. Since the treatment was only simulated, the patient's breathing phase at the start of treatment (starting phase) was unknown and therefore several possible states were simulated, namely end-inhale, end-exhale and two phases in between, 50% inhale and 50% exhale. As a consequence, a band of 64 possible 4D dose distributions (3 fields at 4 starting phases) resulted from the simulation per patient for each fraction. For the fractionated treatment, the start phase of the patient was randomly chosen according to the probability distribution given by the individual breathing pattern. To take into account the unknown starting phase of the patient, 100 different possible combinations of 33 individual fractions were calculated.

Alternative target concept

Target concepts for PBS PT are not well established considering the uncertainties of treatment delivery. Thus, in comparison to the described simple planning target approach (in the following referred to as iGTV/HU approach), the beam-specific PTV concept presented by Knopf et al. (14) was used for 30 patients. This approach takes the data of all 4DCT phases to generate a target contour based on the tumour volume which is adapted for density and position changes due to motion in the beam path.

Anatomical and motion changes during treatment

Additionally, changes in the tumour volume, motion and the general anatomy are of high concern in lung cancer treatment as they could lead to very large changes in the PT dose distribution (15). For two patients of the analysed cohort, control 4DCTs were taken three to four weeks after the first 4DCT, due to clinical reasons. These datasets were used to perform additional 4D dynamic dose calculations, considering changes in motion, anatomy and breathing pattern occurring over the treatment course.

Evaluated were the dose parameter differences (4D Parameter - 3D parameter) ΔV90, ΔV95, ΔV98, ΔD98, ΔD2, ΔV107 and ΔV110 of the PTV on the planning CT phase. The parameter differences were checked for statistical significance based on two-sided t-tests with a significance level of 0.05.

Results

4D dynamic dose calculation

The main tumour motion direction was cranio-caudal, with almost 50 % (19 out of 40) of the patients having a maximum tumour motion amplitude of less than 5 mm. The starting phase had a large high influence on the 4D dynamic dose distribution. As a

consequence, the dose distortion per fraction could range from negligible to large depending on that starting phase of treatment. In general, the magnitude and the range of the dose distortion depended on the maximum motion amplitude. Patients with motion below 5 mm had an average dose degradation in terms of V95 and V98 coverage reduction by -2 % and -5 % (absolute difference) and a reduction of the dose minimum assessed by ΔD98 of -0.0Gy(RBE). However, in single cases the dose degradation could reach ΔV95 of -10 to -20 %. Compared to that, for patients with motion above 5 mm, average dose degradations were -13%, -26% and -0.1Gy(RBE) for ΔV95, ΔV98 and ΔD98 with largest degradations of up to -60% for ΔV95. Similarly, the increase in overdose in the tumour volume was in general small for patients with motion amplitudes below 5 mm, but again in single cases large deviations were found. However, even for patients with large motion amplitudes, scenarios existed in which the dose degradation was rather small. The dose degradation in terms of ΔV95 for all 4D dynamic dose distribution scenarios per patient are given in Figure 1, median dose degradations for the analysed parameters for patients grouped according to their motion amplitude can be found in Figure 2.

Considering that usually a fractionated treatment lasts about 6 weeks, the dose degradation is substantially reduced compared to a single fraction treatment since the patient breathing phase is not controlled at treatment start. However, in the cases of motion amplitudes above 5 mm, no acceptable dose distributions could be achieved by simple fractionation with average ΔV95 of -4%. Furthermore, up to now it is unclear how inhomogeneous dose distributions per fraction might negatively influence the patient's outcome despite acceptable fractionated dose distributions. Dose discrepancies of about 10 % from the prescribed dose were estimated to have negligible impact (16), thus V90 differences might be of large relevance. For patients with motion amplitudes

below 5 mm, V90 was on average 100% for all 4D dynamic dose distributions with a worst case of -1%, while for patients with larger motion amplitudes a reduction of V90 by -2% on average with up to -7% was found. This supports the hypothesis that patients with small tumour motions below 5 mm could be treated satisfactorily with PBS PT free-breathing without taking additional motion mitigation measures.

Alternative target concept

A comparison between the two target volume concepts is shown in Figure 3, depicting median dose degradations per motion group. Using the beam-specific treatment volume approach, the dose distortions for the single fractions do not change considerably. As the dose distortions are mainly caused by the interplay effect which is a consequence of spot motion versus tumour motion, a relatively small change in the tumour contour will have a small impact on the spot positioning and order. Thus, the dose distribution will not change to a large degree (average ΔV95 of -13% versus -11% for iGTV/HU approach versus beam-specific PTV). However, for a fractionated treatment, where the interplay effect will play a less pronounced role, the use of this target concept might play an important role. In almost all patient cases, the dose distortion was reduced by using this contour approach for treatment planning. However, in cases where large dose distortions already occurred throughout the tumour volume in a single fraction because of the interplay effect, the target volume construction could not increase the dose coverage to an acceptable level (persisting average ΔV95 of -4% versus -2% for iGTV/HU approach versus beam-specific PTV).

Anatomical and motion changes during treatment

The re-evaluation of the dose with control 4DCTs was done for two patients, labelled A and B. An overlay of the CT images and the evaluation of the dose distribution in the

planning and the control 4DCT are given in Figure 4. For patient A an almost acceptable level of dose degradation was found in the simulation of the fractionated treatment based on the planning 4DCT. The recalculation on the control 4DCT, however, showed a significant change in tumour motion amplitude of more than 5 mm in this patient accompanied by a change of his breathing pattern. This motion amplitude change had a profound impact on the simulated dose delivery as the tumour moved out of the irradiated volume leading to a large underdosage and thus a completely unacceptable dose distribution. Patient B had a tumour motion amplitude change of about 2 mm leading to reduced dose coverage of the target and a broadening of the estimated possible dose degradations compared to the initial planning 4DCT scenarios. These findings underline the importance of re-evaluations of dose distributions on changed anatomy throughout the treatment course.

Discussion

The magnitude of motion was described as insufficient for the prediction of the magnitude of the interplay effect (3, 9,17). This was confirmed by our patient cohort. A larger motion amplitude did not necessarily mean a higher dose degradation by the interplay effect, but gave a general trend and could be used as indicator on how to proceed for motion mitigation and treatment planning. The evaluation of the 4D dynamic dose distribution of 40 patients simulated for free-breathing treatment without motion mitigation showed an acceptable level of dose degradation for patients with motion amplitudes below 5 mm. For patients with motion amplitudes above 5 mm, in general more profound dose deteriorations were found per fraction, which also translated into persisting dose degradation in a fractionated treatment simulation. Thus, for patients with larger motion amplitudes above 5 mm, motion mitigation techniques need to be implemented, while patients with small motion amplitudes below 5 mm

could be treated with the presented approach. In our patient cohort, consisting of patients with small lesions only, about 50% of the patients had small tumour motion amplitudes below 5 mm. Motion analyses of lung cancer patients with larger tumour sizes showed an even larger proportion of patients with such small motion amplitudes (18). Thus, this is a relevant proportion of patients who can be treated with a simple PBS PT approach.

However, changes in tumour motion amplitude and position, which might occur under treatment, either because the patient relaxes, and thus changes his breathing pattern (as it might have been the case for patient A), or potentially due to tumour shrinkage leading to increased mobility, might have a large impact on the dose distribution. Moreover, relevant anatomical changes could occur during treatment which additionally impact the dose distribution (15).

The use of the more sophisticated target volume including the uncertainties caused by range changes due to motion, could relevantly improve the dose coverage. However, since the dose coverage was already good with the simpler approach using the iGTV/HU approach, for patients with small amplitudes below 5 mm this concept might not be needed for this subgroup of patients. On the other hand, the beam-specific target approach could also include additional uncertainties due to range and set-up, leading to a more robust treatment plan for these uncertainties (19). This was not simulated in the presented study, but might be important especially for full IMPT treatment. For patients with larger tumour motion amplitudes, the inclusion of the motion into the beam-specific target concept could be an approach to increase tumour coverage. This is especially the case when using rescanning as motion mitigation technique, which tends to decrease the interplay effect, but can in principle not reduce dose changes due to range uncertainties.

If (layered) rescanning are deemed insufficient for the patients with larger motion(6), additional approaches should be applied, such as breath sampling, gating or delivery sequence optimisation (9,20,21). Furthermore, the use of information about the changes in water-equivalent thickness ΔWET along the beam path for beam direction choice was proposed (22). However, the capability of a treatment system to interrupt the application of a spot sequence, which is required for gated treatments, might be limited, e.g. for synchrotron-based particle therapy. Changes in the spot delivery sequence, e.g. systematic repositioning of spots, might reduce the resultant interplay effect (20), but could be difficult to implement with current clinical systems. Information about ΔWET is usually based on in-house software and is not yet a standard in commercial treatment planning systems.

Comparisons to other publications analysing the interplay are difficult, since the individual machine parameters have a large impact on the results. Kraus et al. analysed two patient cases with motion amplitudes of about 10 mm and found persisting relevant under- and overdosage in a fractionated treatment (4). In contrast to that, Grassberger et al. found only small relevant effects on minimum and maximum doses in a fractionated treatment for up to 20 mm motion amplitudes when considering fractionated treatment in their patient cohort of 10 patients (5). This underlines the strong dependence on the individual machine and patient characteristics in the analyses of interplay.

Kardar et al. (10) showed reduced coverage for seven patients treated with PBS PT. Similar to our result, the patients with motion amplitudes below 5 mm had less dose degradation than patients with larger motion amplitudes (except in one case). They could also show that the limitation of the maximum deliverable MU per spot which leads to inherent rescanning could improve the dose distribution tremendously. Furthermore, a dependence on the tumour size was found, which could not be

confirmed by us. However, in our study mainly small tumour volumes were analysed which might hamper this comparison. Nevertheless, Li et al. also showed a good agreement between 4D dynamic dose, ie considering the interplay effect, and 4D dose without considering the interplay effect for patients with motion below 5 mm and concluded that 4D dynamic dose distributions might not be required for evaluations (18). However, their simulated spot size was larger than the one used here, which reduces the interplay effect (5). Furthermore, their system inherently used rescanning, which also reduces the interplay effect.

The simulations are limited by several factors: first, all 4D dynamic doses are based on one 4DCT image sequence. Depending on the patients' breathing motion stability, and the relation between reconstruction time and breathing period, the image dataset might contain artefacts. Such artefacts reduce the reliability of the dose calculation. Furthermore, for fractionated treatment we assumed that the motion pattern and the anatomy of the patient do not change throughout the treatment. As seen in the two patient cases with control 4DCT, anatomical and breathing pattern changes will have a relevant impact on the dose distribution, and thus the evaluation here will rather underestimate the dose degradation. In addition, 4DCT was shown to be prone to errors in motion amplitude evaluation, thus the real motion might be underestimated and, as such, its consequences on the dose distribution as well (23). Second, the examined patient cohort consisted of patients intended for stereotactic treatment, who mainly have small tumours and no involved lymph nodes. However, PT is expected to be more important for patients with advanced disease. We expect that the motion amplitude can in principle be used for a treatment approach selection for larger tumours. However, these patients are even more likely to have anatomical changes throughout the treatment and our conclusion, that patients need to be monitored closely for such changes is even

more important. Third, dose calculations were performed with a pencil beam algorithm, which has been shown to be inferior in lung dose calculations. However, the 4D dose assessment by Grassberger et al. (24), in which a Monte-Carlo algorithm was used, gave similar conclusions. Thus, the presented results, although hampered by the reduced accuracy of the pencil beam algorithm, can be used to draw these general conclusions described here. Finally, for a full clinical implementation of PBS PT, all possibly occurring uncertainties should be evaluated in combination including machine, setup, range and motion uncertainties. The additional simulation of setup errors, for example, might further reduce the influence of motion effects due to statistical smoothing. Such a comprehensive evaluation tool is currently in preparation.

Although individual machine parameters impact the magnitude of the interplay effect, the hypothesis that tumours with <5 mm motion amplitude can be treated with PBS PT without additional techniques should hold for many institutions which share similar or larger spot sizes and similar machine timings. This is supported by the results of other groups who showed similar results (4,5,10). Nevertheless, since large changes in anatomy and motion pattern might occur throughout treatment, it is of high relevance and importance to check for these changes to ensure a consistently high-quality treatment.

Conclusion

The feasibility of using pencil beam scanning in free-breathing lung cancer patient treatments was assessed. Tumours with motion amplitudes of below 5 mm can be safely irradiated even with a small spot size. For these patients, a target approach which includes the motion in beam-specific contours is not required according to our results. Changes in tumour motion and patient anatomy should be closely monitored to be able

to adapt the treatment as soon as changes occur.

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Figure 1: Dose degradation in terms of %V95 dose parameter difference per patient between the 4D dynamic dose distribution taking into account the interplay effect and the planned 3D dose. (a) Single fraction dose distribution. (b) Fractionated treatment. Patients are ordered according to their tumour motion amplitude in superior-inferior direction.

Figure 2: Absolute parameter differences (V in % differences, D in Gy(RBE)) of the patient group divided into subgroups with motion amplitudes below (cyan) and above (red) 5 mm. (a) Single fraction dose distribution. (b) Fractionated treatment. * denotes significant differences based on independent t-tests between median values of the patient groups with motion amplitudes below and above 5 mm, significance level of 0.05.

Figure 3: Absolute parameter differences of the 30 patients evaluated for the different PTV strategies iGTV/HU (cyan, red) and beam-specific PTV (blue, dark red) divided into subgroups with motion amplitudes below (cyan, blue) and above (red, dark red) 5 mm. (a) Single fraction dose distribution. (b) Fractionated treatment. * denotes significant differences based on paired t-tests between median values of the patient groups with motion amplitudes below and above 5 mm, significance level of 0.05.

Figure 4: (a) Anatomy change of the two patients with control 4DCT data (exhalation phase) shown as overlay of a sagittal image. (b) DVH of the target for the 64 evaluated single fraction dose scenarios. Magenta: original planning 4DCT, green: control 4DCT.