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Original Research Article

On-line dose-guidance to account for inter-fractional motion during proton therapy☆

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ABSTRACT

Background and purpose: Proton therapy (PT) of extra-cranial tumour sites is challenged by density changes caused by inter-fractional organ motion. In this study we investigate *on-line* dose-guided PT (DGPT) to account inter-fractional target motion, exemplified by internal motion in the pelvis.

Materials and methods: On-line DGPT involved re-calculating dose distributions with the isocenter shifted up to 15 mm from the position corresponding to conventional soft-tissue based image-guided PT (IGPT). The method was applied to patient models with simulated prostate/seminal vesicle target motion of ± 3, ± 5 and ± 10 mm along the three cardinal axes. Treatment plans were created using either two lateral (gantry angles of 90°/270°) or two lateral oblique fields (gantry angles of 35°/325°). Target coverage and normal tissue doses from DGPT were compared to both soft-tissue and bony anatomy based IGPT.

Results: DGPT improved the dose distributions relative to soft-tissue based IGPT for 39 of 90 simulation scenarios using lateral fields and for 50 of 90 scenarios using lateral oblique fields. The greatest benefits of DGPT were seen for large motion, e.g. a median target coverage improvement of 13% was found for 10 mm anterior motion with lateral fields. DGPT also improved the dose distribution in comparison to bony anatomy IGPT in all cases. The best strategy was often to move the fields back towards the original target position prior to the simulated target motion.

Conclusion: DGPT has the potential to better account for large inter-fractional organ motion in the pelvis than IGPT.

1. Introduction

Proton therapy (PT) is currently being investigated for a number of tumour sites due to the favourable depth dose characteristics of protons. However, the sharp distal dose fall-off in proton beams makes this treatment modality sensitive towards density changes. A study of the robustness of intensity modulated PT (IMPT) plans showed that small inter-fractional translational set-up errors for *cranial* tumours degraded the dose distribution severely, with the extent depending on beam directions [1]. Treatment of *extra-cranial* tumour sites is an even greater challenge since larger anatomical changes may occur during the course of treatment, originating from weight loss, tumour shrinkage and/or inter-fractional motion and set-up/posture changes [2–8]. The dose distribution may therefore deteriorate, with inferior target coverage and increased doses to the normal tissues [9]. It has been shown that selecting beam angles from variations inside the beam path in tissue density or water equivalent path length may reduce the impact of motion for IMPT [10–14].

The main approach to account for inter-fractional variation in radiotherapy (RT) is on-line image-guidance, based on imaging of fiducial markers, bony anatomy and/or soft tissue, with the patient aligned in treatment position. However, we and others have shown that image-guided PT (IGPT) have difficulties in avoiding motion-induced target dose degradations [5,15–17]. Vargas et al. investigated the impact of prostate motion using PT and found dose coverage to be adequate for small motion (less than 5 mm), while beam realignment improved coverage for larger displacements [18].

The concept of dose-guided RT (DGRT) was proposed as an alternative to image-guidance based on reference anatomy by Cheung et al. [19]. Haehnle et al. later explored DGRT using pareto fronts for selection of the most beneficial isocenter positioning in treatment of prostate as well as head and neck cancer [20]. Cheung et al. [21] further applied

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dose-guidance to PT (DGPT) exploring pre-calculated isocenter shifts to account for anatomical changes in lung cancer patients and found that dose-based isocenter adjustments of passive scattering proton fields was able to improve the dose distributions compared to IGPT. Building upon this work we here propose the concept of on-line DGPT, which involves the use of on-line dose re-calculations of possible isocenter shifts to find the optimal re-positioning of the patient without the use of pre-calculated isocenter shifts.

The aim of the study was therefore to investigate the potential of on-line DGPT to restore target coverage and minimise the normal tissue dose compared to IGPT, exemplified by inter-fractional target motion in the pelvis. We also wanted to demonstrate whether beam angle selection of robust angles reduced the possible benefit of on-line DGPT, and we therefore explored the method for two different PT beam configurations.

2. Materials and methods

2.1. Dose-guidance

On-line DGPT (Suppl. Fig. 1) was explored by calculating multiple dose distributions with the isocenter shifted an additional ± 1, ± 2, ± 3, ± 5, ± 10 and ± 15 mm along the three cardinal axes away from the field position used for the soft-tissue based IGPT re-calculation, giving a total of 36 DGPT dose distributions for each simulated inter-fractional motion (Suppl. Fig. 2). We also counted the position corresponding to soft-tissue based IGPT as a possible DGPT alternative. We focused on the ability of DGPT to counteract the effects of inter-fractional motion without performing an exhaustive search across all possible shifts, and without any consideration of dose calculation times. Conventional soft-tissue based IGPT was investigated by shifting the plan isocenter the same amount as the simulated motion followed by plan re-calculation. A DGPT dose distribution was found superior if it resulted in a better target coverage compared to soft-tissue based IGPT, for all three targets and a lower dose to the normal tissue (criteria given in 'Data analysis'). The same constraints were used when investigating bony anatomy based image-guidance. Results from bony anatomy based IGPT was also compared to DGPT using the same constraints, if an improved DGPT plan had been found.

2.2. Patient models and motion simulations

Five patient models were created using a planning CT (pCT) and four repeat CTs (rCTs) of a patient with locally advanced prostate cancer. Air, soft tissue and bones were delineated in all five scans and the Hounsfield Units (HUs) were afterwards overwritten to air, water and the average of bone for the specific patient to enable motion simulations and to isolate the effects of inter-fractional target and patient motion. The rCTs were included in the study to investigate the effects of surface and posture changes.

The prostate planning target volume (PTV) was created in the pCT scan by expanding the prostate clinical target volume (CTV-p) 7 mm in all directions, except in the superior-inferior direction, where 9 mm was used. The CTVs of the lymph nodes (CTV-ln) and seminal vesicles (CTV-sv) were expanded by 5 mm and 8 mm in the superior-inferior direction to create the corresponding PTVs. These margins were identical to the margins used clinically when treating prostate cancer patients with photon-based RT at Aarhus University Hospital. The normal tissue in each CT was defined as the complete patient volume (i.e. the body contour) with the CTVs subtracted.

Inter-fractional motion was simulated by moving the prostate and SV PTVs ± 3, ± 5 and ± 10 mm together along the three cardinal axes using MIM (MIM Software Inc., Cleveland, Ohio, US) and MATLAB (MATLAB and Statistics Toolbox Release 2017b, The MathWorks, Inc., Natick, Massachusetts, US), while keeping the lymph node (LN) PTV stationary in the patient models, resulting in 90 scenarios of composite prostate and SV motion (Suppl. Fig. 2).

2.3. Treatment planning

Two IMPT plans using multi-field optimisation were created (Eclipse treatment planning system (TPS), Varian Medical Systems, Palo Alto, CA, USA) on the pCT, with one using two lateral opposed beams (gantry angles 90°/270°) and the other using two lateral oblique beams (gantry angles 35°/325°) identified in a previous inter-fractional robustness study [14] (Suppl. Fig. 3). The prescribed doses were 78 Gy in 39 fractions for the prostate PTV and 56 Gy in the same number of fractions for the combined LN and SV PTV (planning constraints according to in-house photon-based clinical protocols; Suppl. Table A). A soft-tissue and a bony anatomy based rigid registration were performed between the pCT and rCTs before transferring the IMPT plans to the rCTs. The soft-tissue registration was based on the isocenter of the prostate using MIM. Bony anatomy IGPT was explored in the rCTs (i.e. the fields were stationary with respect to bony anatomy).

To relate the effect of DGPT to dose-guidance in conventional photon-based RT, we also created a volumetric modulated arc therapy (VMAT) plan on the pCT. The VMAT plan used two 15MV arcs, one arc from 181° to 179° in a clockwise rotation and the other arc from 179° to 181° counter clockwise. Dose-guidance with VMAT was investigated only for 10 mm anterior motion.

2.4. Data analysis

The resulting DGPT and IGPT dose distributions were evaluated on the CTV coverage using the volume receiving 98% of the prescribed dose (V98%) for all targets, while the normal tissue was evaluated based on the maximum dose to 1 cc (D1cc).

We particularly investigated if the dose distributions with DGPT had better V98% coverage of all three CTV targets and a lower D1cc to the normal tissue compared to the soft-tissue based IGPT dose distribution. If this was fulfilled by more than one DGPT dose distribution, the distribution with the highest prostate CTV coverage was chosen.

3. Results

Improvements in dose distribution using DGPT varied between the two field configurations and the extent of motion simulated. For each of the 30 simulations with 3 mm, 5 mm and 10 mm motion using lateral fields, DGPT gave a better dose distribution compared to soft-tissue based IGPT 7, 11 and 21 times. For 6, 11 and 19 times it was best to move the fields back towards the isocenter of the CTV-p at its original placement prior to simulated target motion (the uncorrected position prior to image-guidance), respectively. For the 24 simulations using bony anatomy based IGPT in the rCTs, DGPT improved the dose distribution 6, 8 and 17 times. For the lateral oblique fields it was best to move the fields back for 8, 9 and 13 times out of 17, 17 and 16 times for 3, 5 and 10 mm, where DGPT gave a better dose distribution than soft-tissue based IGPT. For the 24 simulations using bony anatomy based IGPT, DGPT was superior 13, 11 and 11 times.

DGPT improved the dose distribution from lateral fields beyond soft-tissue based IGPT for a total of 39 out of 90 shifts; 31 of these shifts occurred in the rCTs, with DGPT being superior to both soft-tissue and bony anatomy based IGPT for all these shifts. The fields were moved towards the uncorrected position in 92% of the shifts where DGPT were superior to soft-tissue based IGPT. The greatest improvement of DGPT compared to soft-tissue based IGPT occurred for 5 and 10 mm inter-fractional motion in the anterior direction when lateral fields were applied (Figs. 1 and 2). Here target coverage increased when using DGPT instead of soft-tissue based IGPT with a median of 13, 9 and 3 percentage points for the CTV-p, CTV-sv and CTV-ln. At the same time

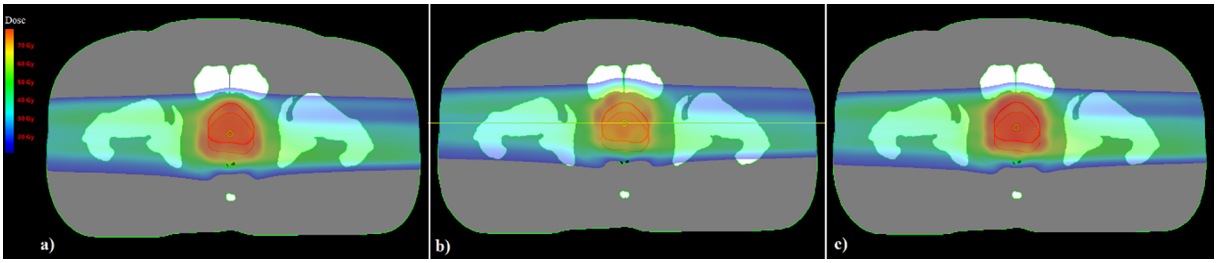

Fig. 1. Dose distribution for 10 mm anterior motion for a) bony based IGPT, i.e., the plan was moved from the pCT to the rCT based on bony anatomy, b) soft-tissue based IGPT, i.e. the fields are at the isocenter of the moved target after a soft-tissue registration and c) DGPT, where the preferred dose distribution have been chosen, which in this case is when the fields are moved 5 mm posterior towards the uncorrected position prior to IGPT.

the normal tissue doses were reduced with DGPT. Similarly, for 5 and 10 mm motion in the inferior direction, DGPT resulted in a median increase compared to soft-tissue based IGPT of 3 percentage points for the CTV-sv (Suppl. Mat. A). For 10 mm inferior motion in the pCT, a reduction in D1cc for the normal tissue of 11 Gy was found. Applying DGPT to counteract inter-fractional motion in the posterior, superior, left and right directions had small or no improvements beyond IGPT (Suppl. Mat. A).

DGPT gave in all cases better dose distributions than bony anatomy based image-guidance. However looking at the three targets separately the doses were better with bony anatomy image-guidance for anterior shifts using lateral fields for 11, 8 and 2 out of 12 rCTs for the CTV-p, CTV-sv and CTV-ln, respectively. The median target dose improvement across all 12 rCTs for each target was 2, 6 and −0.4 percentage points. For posterior motion using lateral fields a large dose degradation were seen in almost all rCTs using bony anatomy based IGPT with a median decrease of 12 percentage points and 24 percentage points for CTV-p and CTV-sv (Fig. 2).

For the lateral oblique fields, DGPT gave a better dose distribution compared to soft-tissue based IGPT in 50 out of 90 times, and in 60% of the shifts where DGPT were superior to soft-tissue based IGPT it was better to move the fields back towards the uncorrected position. A total of 35 out of the 50 shifts occurred in the rCTs and for all 35 shifts DGPT gave a better dose distribution compared to both soft-tissue based IGPT and bony anatomy based IGPT. However, once where DGPT could not improve the dose distribution compared to soft-tissue based IGPT, bony anatomy based IGPT were found superior to soft-tissue based IGPT, which occurred for 10 mm right shift in rCT no. 3. The greatest target coverage improvements from soft-tissue based IGPT to DGPT occurred for 3 mm inferior motion, where a target increase of 10 percentage points were seen for the CTV-sv in one of the rCTs (Suppl. Mat. B). A large reduction in normal tissue doses were seen for both 3, 5 and 10 mm motion in the pCT for inferior motion (median decrease of 26 Gy with DGPT). A median increase of 10, 8 and 6 percentage points for the CTV-p, CTV-sv and CTV-ln occurred in two of the five CTs for posterior motion (Fig. 3). For motion to the right, an increase of 9 and 17 percentage points were seen for the CTV-p in the pCT for 5 and 10 mm and in the latter, an 8 percentage points increase occurred for the CTV-ln (Suppl. Mat. B). Motion in the left, superior and anterior directions showed small or no improvements using DGPT (Suppl. Mat. B).

A DGPT plan was found superior to soft-tissue based IGPT 9 out of the 18 shifts that was made in the pCT, compared to 31 times out of 72 shifts in the rCTs. For the same simulated motion using lateral fields, the preferred DGPT shift in the pCT and rCTs were identical only 5 times out of the 9 and 31 times DGPT was found superior. For the lateral oblique fields a DGPT plan was found superior 15 and 35 times in the pCT and rCTs, respectively. Similar to the lateral fields the preferred shifts for the same simulated motion in the pCT and rCTs were identical 5 times.

When DGPT gave a superior dose distribution compared to soft-tissue based IGPT, each target often had a V98% coverage below the value from the original (Table 1). Only in one distribution had all three targets a V98% value similar or higher than in the original pCT plan, which occurred for 5 mm anterior shift using lateral fields. It was most often the CTV-sv that had a similar coverage in both the pCT and rCTs for both field configurations and motion simulations.

In the investigation of dose-guidance for VMAT using 10 mm anterior motion, minor improvements from soft-tissue based and bony anatomy based IGPT to DGPT was found. The median increase from soft-tissue based IGPT to DGPT was 12, 2 and 4 percentage points for CTV-p, CTV-sv and CTV-ln using two lateral proton fields and 0.5, 0 and 2 percentage points for two lateral oblique proton fields, while it was 1, 2 and 4 percentage points using VMAT. For the normal tissue a median decrease of 6 Gy, 3 Gy and 1 Gy were found for the lateral proton fields, lateral oblique proton fields and VMAT, respectively (Table 2). The targets median increases using bony anatomy based IGPT to DGPT were −1.5, 0.5 and 0 percentage points for lateral fields and 1, 4.5 and −5.5 percentage points for lateral oblique fields. A median decrease of 0.5 and −9 percentage points occurred for the normal tissue for the lateral proton fields and lateral oblique proton fields (Table 2).

4. Discussion

In this study we have investigated the use of *on-line* dose-guided isocenter shifts to account for inter-fractional motion during PT – in comparison with conventional image-guidance – with the aim of restoring target coverage and reducing normal tissue doses. We found that DGPT improved the dose distributions, but that the degree of improvement depended on the extent of motion simulated and the field configuration studied. In general, we found that shifting the fields back towards the uncorrected position (pre image-guidance) resulted in an improved dose distribution. This implies that soft-tissue based image-guidance might 'over-correct' the shifts derived only from the target image and that ideal shifts for PT will depend on both the target position and the patient's anatomy (in particular the bony anatomy). However DGPT was better than bony anatomy based image-guidance in all cases with the constraints we had chosen. In one case where dose-guidance did not improve the dose distribution beyond soft-tissue based IGPT, bony anatomy based image-guidance gave a better target coverage.

Target coverage is a main concern in PT, however we have shown that on-line DGPT can improve target dose, although the increase may not always be sufficient to obtain clinically acceptable dose coverage according to planning constraints; e.g. for posterior motion using lateral fields, often no or only small target improvements were found, due to the dose gradient towards the rectum. The same was seen for left and right motion using lateral fields, since the targets were moved along the beam path. The applied PTV margins help secure the target coverage for small inter-fractional motion and dose-guidance may therefore not improve the dose distribution in these cases. When DGPT improved the dose distribution it was often best to move the fields back towards the uncorrected position minimising the density changes caused by bony anatomy. Vargas et al. also found realignment of proton beams to give a modest improvement in CTV coverage for prostate motion smaller than

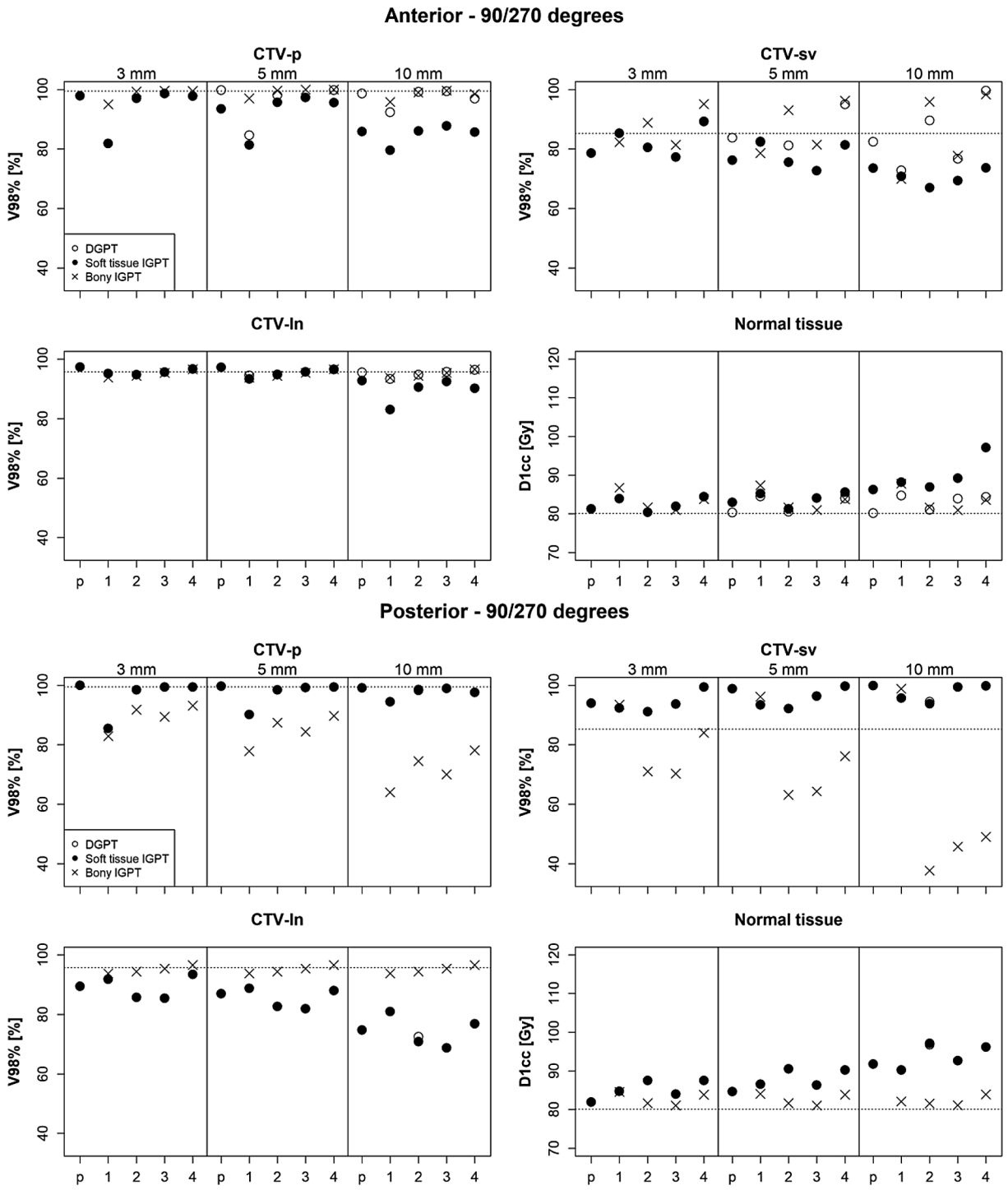

Fig. 2. V98%/D1cc for the soft-tissue (black circles) and bony anatomy (black crosses) based IGPT plans and the best DGPT (open circles) dose distribution for the CTVs and normal tissue using two lateral fields. Motion of 3, 5 and 10 mm in the anterior and posterior direction in all CT-scans were simulated (pCT and four rCTs). The vertical line depicts the V98% value from the original pCT plan. Normal tissue was defined as everything except CTV targets and bones.

the PTV margin [22]. When the fields were moved back to the uncorrected position, the target dose improved due to the applied PTV margin. It also improved normal tissue sparing, since the high dose distribution is aligned better to the targets, which allows the dose fall-off to be appropriately aligned to the nearby organs.

The choice of beam angles in PT is important not only for normal tissue sparing but also for increasing plan robustness (i.e. securing target coverage), which combined with DGPT may reduce the need for re-planning. In our study large dose deterioration occurred for 10 mm posterior motion using lateral oblique fields. These could not be fully resolved using DGPT, although the dose distribution improved substantially. The large dose deterioration was due to the dose gradient towards the rectum. However, in other cases DGPT improved the target coverage sufficiently, which e.g. was seen in some of the CTs for simulated motion to the right. This opens up for the possibility to treat patients using lateral oblique proton fields, which may be beneficial for patients with e.g. hip prosthesis or who have been irradiated through their hip previously [23]. Lateral oblique fields were also explored in a study by Moteabbed et al. with focus on the impact of setup and anatomical variations in prostate cancer, showing that the field

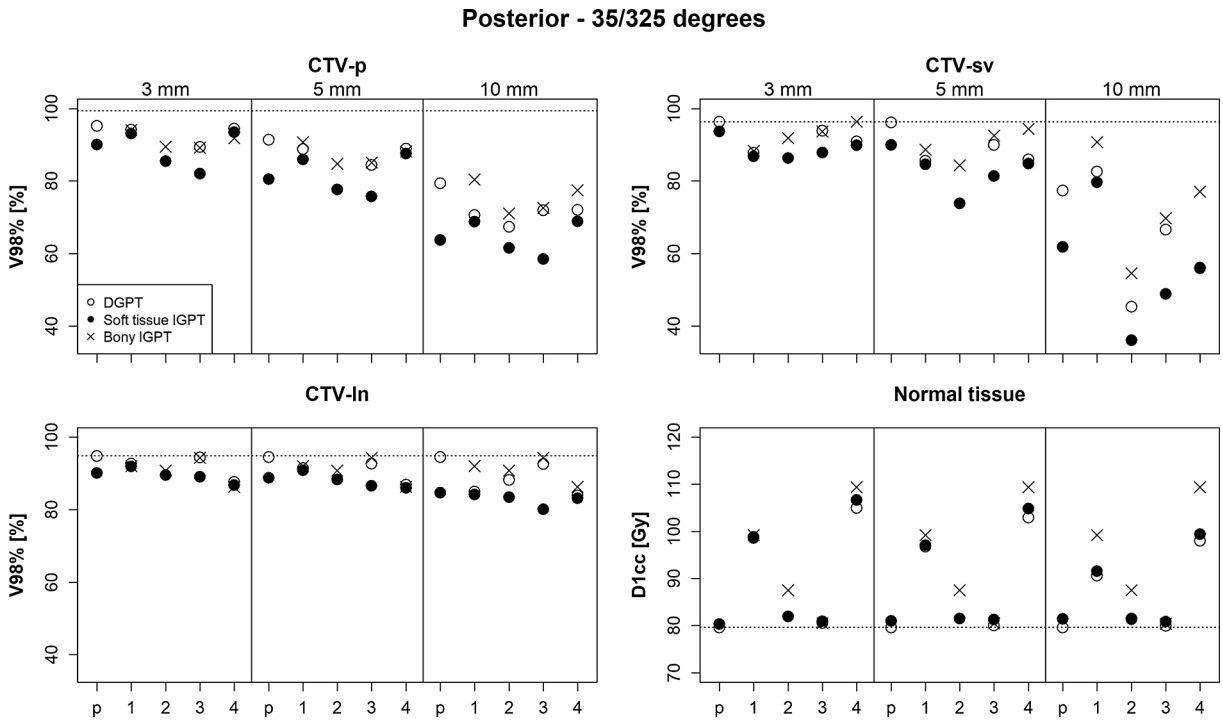

Fig. 3. V98%/D1cc for the soft-tissue (black circles) and bony anatomy (black crosses) based IGPT plans and the best DGPT (open circles) dose distribution for the CTVs and normal tissue using two lateral oblique fields. Motion of 3, 5 and 10 mm in the posterior direction in all CT-scans were simulated (pCT and four rCTs). The vertical line depicts the V98% value from the original pCT plan. Normal tissue was defined as everything except CTV targets and bones.

Table 1
The percentage of motion simulations in all CT-scans, where the three CTVs had a target coverage higher than in the original pCT for ± 3 mm, ± 5 mm and ± 10 mm along the three cardinal axes. The columns shows the percentage for a target coverage higher than in the original pCT using DGPT compared to soft-tissue based IGPT for each target.

	CTV-p [%]	CTV-sv [%]	CTV-ln [%]
90°/270°			
± 3 mm	12.5	62.5	25
± 5 mm	27	45.5	45.5
± 10 mm	0	9.5	9.5
35°/325°			
± 3 mm	6	29	0
± 5 mm	18	35	6
± 10 mm	6	31	0

Table 2
V98% for the three targets and D1cc for the normal tissue (all tissue with the CTVs subtracted) for a 10 mm anterior simulated motion. The results are shown for the soft-tissue based and bony anatomy based IGPT plans and best DGPT dose distribution for both configurations in all scans and for photons in the pCT. An x indicates that no better DGPT dose distribution was found.

10 mm Anterior	CTV-p (V98%) [%]	CTV-sv (V98%) [%]	CTV-ln (V98%) [%]	Normal tissue (D1cc) [Gy]
90°/270°	Bony IGPT | Soft-tissue IGPT | DGPT	Bony IGPT | Soft-tissue IGPT | DGPT	Bony IGPT | Soft-tissue IGPT | DGPT	Bony IGPT | Soft-tissue IGPT | DGPT
pCT	x | 86 | 99	x | 74 | 83	x | 93 | 96	x | 86 | 80
rCT1	96 | 80 | 92	70 | 71 | 73	94 | 83 | 93	88 | 88 | 85
rCT2	99 | 86 | 99	96 | 67 | 90	94 | 91 | 95	82 | 87 | 81
rCT3	100 | 88 | 99	78 | 70 | 77	95 | 93 | 96	81 | 89 | 84
rCT4	99 | 86 | 97	98 | 74 | 100	97 | 90 | 96	84 | 97 | 84
35°/325°				
pCT	x | 98 | 98	x | 100 | 100	x | 90 | 91	x | 97 | 95
rCT1	95 | 97 | 97	81 | 92 | 92	92 | 79 | 79	99 | 107 | 107
rCT2	98 | 99 | 100	96 | 100 | 100	91 | 85 | 88	88 | 102 | 98
rCT3	99 | 98 | 98	94 | 99 | 99	94 | 90 | 90	81 | 91 | 91
rCT4	96 | 96 | 96	99 | 100 | 100	86 | 79 | 79	109 | 110 | 110
VMAT				
pCT	x | 97 | 98	x | 95 | 97	x | 87 | 91	x | 83 | 82

configuration was sensitive towards inter-fractional motion, causing target underdosage [24]. However in another study of pelvic LN irradiation with protons, lateral oblique fields were found robust towards density changes [14].

The concept of on-line dose-guidance builds on the work by Cheung et al., who suggested off-line dose-guidance for (passive scattering) PT. Their workflow was based on exhaustive dose pre-calculations [21]. In our study we have used multi-field optimised IMPT which improves the dose conformity, yet may make the plans less robust towards inter-fractional motion. On-line dose-guidance has considerable implications for the implementation into the clinical workflow in regards to software integration such as automatic contouring and scatter-correction of CBCTs. Several groups are working on the latter making it possible to calculate more accurate proton dose distributions [25–27]. Manual contouring is time consuming and organ motion can occur in the time it takes to contour the relevant structures, hence fast contouring is necessary [26–29]. Regarding on-line dose calculations, the TPS (Eclipse) used in this study can be used to search for the optimal field position along the three cardinal axes. It took approximately three minutes to calculate 36 DGPT dose distributions; however with a modern processor a 1.5x speed-up could possibly be achieved. Pareto sliders are also a possibility, which have been implemented and investigated by Haehnle et al. [20], who concluded that an optimised dose-guidance workflow can be performed in minutes.

Different from previous dose-guidance studies, we looked at simultaneous coverage of three targets. We found it difficult to get a sufficient coverage of all targets at once, similar to Thörnqvist et al.,

who also found it difficult to cover all targets no matter the choice of alignment method or the use of wider margins [5]. In the case where target coverage cannot be restored a full-fledged re-planning or the use of a back-up plan might be needed. The constraints we used to determine when a plan is acceptable are very strict. Bony anatomy based IGPT could be preferred compared to dose-guidance for certain simulated shifts if the constraints were more flexible, e.g. for anterior motion, where an improved dose to the prostate and seminal vesicles was observed, with a slightly lower dose to the lymph nodes. In addition, our normal tissue dose constraints focusing on maximum dose may also not be suitable for all OARs in the pelvis.

In this study we have used simplified patient models and our results do therefore not take the full complexity of organ motion and tissue heterogeneity into account. Further investigations on volumetric (CT) images using a larger patient cohort would therefore be warranted. However, even using simplified patient anatomies, we have shown that posture/surface changes and inter-fractional motion may have an impact on the dose distributions.

Inter-fractional motion may also be accounted for by using robust optimisation, where uncertainties in range and patient set-up are taken into account during plan optimization and no PTV margins are used [30,31]. A study found robust optimisation to provide robust target coverage for different tumour sites [32]. However robust optimised plans are less conformal than multi-field optimised IMPT plans [33] and most robust optimisation implementations do not take anatomical changes per se (as seen in online volumetric imaging) into consideration. However, DGPT and robust optimisation have the potential both individually and combined to reduce the need for a full-fledged adaptive re-planning during treatment, which has strong implications for the planning and treatment workflow (including pre-treatment plan verifications).

In conclusion, this study showed that DGPT can improve the target and normal tissue doses in around half of the scenarios for both field configurations investigated. However, it was difficult to restore target coverage in all targets at once. In addition, we found that it was mainly for large simulated motion that dose deterioration occurred and it was often best to shift the fields back towards the uncorrected position. Further studies are needed to show if the potential of DGPT found in this study transfers across to an even more clinically realistic scenario.

Acknowledgements

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Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2018.11.009.

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