



Original Research Article

A biological modelling based comparison of radiotherapy plan robustness using photons vs protons for focal prostate boosting



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A B S T R A C T

Background and purpose: Focal tumour boosting is currently explored in radiotherapy of prostate cancer to increase tumour control. In this study we applied dose response models for both tumour control and normal tissue complications to explore the benefit of proton therapy (PT) combined with focal tumour boosting, also when accounting for inter-fractional motion.

Materials and methods: CT scans of seven patients fused with MRI-based index volumes were used. Two volumetric modulated arc therapy (VMAT) plans were created for each patient; one with conventional dose (77 Gy) to the entire prostate, and one with an additional integrated boost (total dose of 95 Gy) to the index lesion. Two corresponding intensity modulated PT (IMPT) plans were created using two lateral opposing spot scanning beams. All plans were evaluated using an MRI-based tumour control probability (TCP) model and normal tissue complication probability (NTCP) models for the rectum and bladder. Plan robustness was evaluated using dose re-calculations on repeat cone-beam CTs.

Results: Across all plans, median TCP increased from 86% (range: 59–98%) without boost to 97% (range: 96–99%) with boost. IMPT plans had lower rectum NTCPs (e.g. 3% vs. 4% for boost plans) but higher bladder NTCPs (20% vs. 18% for boost plans), yet only the bladder NTCPs remained different in the cone beam CT-based re-calculations.

Conclusions: Focal tumour boosting can be delivered with either VMAT or protons, and increases the predicted TCP. The small benefit of IMPT when assessing the planned dose distributions was lost when accounting for inter-fractional motion.

1. Introduction

Radiotherapy (RT) is an important treatment modality for both localised and locally-advanced stages of prostate cancer [1,2]. Around 35% of intermediate- and high-risk prostate cancer patients present with disease relapse following RT, but trials have shown that this rate can be reduced by RT dose escalation [3–5]. It has also been shown that local recurrences tend to occur at the location of the macroscopic tumour [6,7]. The emerging concept of focal tumour boosting is currently explored in clinical prostate cancer trials [8–10] and involves a radiation boost limited to the macroscopic tumour within the prostate to improve local control without increasing the risk of toxicity of the

organs at risk (OARs). Focal boosting of the prostate may become established clinical practise, in turn, making it essential to explore the optimal treatment approach and modality.

The on-going focal prostate tumour boosting trials are performed using photon-based RT. However, proton therapy (PT) may be advantageous due to the physical properties of charged particles, with a sharp increase in depth prior to reaching their well-defined range. Using photons, dose conformity surrounding the tumour is achieved by a re-distribution of low to intermediate doses to a greater volume of the normal tissues. A highly conformal dose around the target volume can be achieved with fewer fields when using PT, which in turn reduces the integral dose thus avoiding the low dose bath [11–13].

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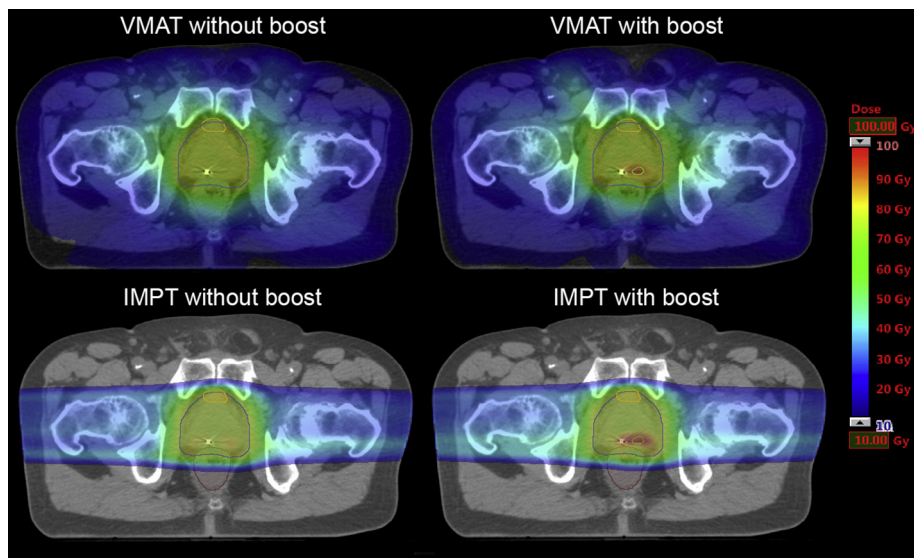


Fig. 1. Dose distributions. Dose distributions for each modality and arm for the same patient.

Recent treatment planning studies have compared the feasibility of focal boosting in different RT modalities such as volumetric modulated arc therapy (VMAT), intensity-modulated proton therapy (IMPT) and brachytherapy, and found that this was equally feasible for all modalities up to a certain dose. Andrzejewski et al. found that although OAR doses were higher using focal boosting than for standard treatment, the risk levels were reasonably low for all these three modalities [14]. Kuang et al. investigated focal boosting with VMAT and concluded that planning objectives and dose constraints could be met in the 30 included prostate patients [15]. Yeo et al. compared protons with intensity-modulated RT (IMRT) in a focal boost scenario and found that protons delivered comparable doses to targets and spared normal tissues from intermediate-to-low doses better than IMRT [11].

Internal anatomical variations can have a large impact on the delivered proton dose distributions [16,17], in particular for focal boost treatments, shifting the high dose volumes away from the tumour and possibly into the normal tissues and ORs [11,14,15]. However, none of the previous focal boosting planning studies investigated the robustness towards inter-fractional motion for VMAT or IMPT [11,14,15]. Furthermore, biological models might be particularly useful when evaluating the potential clinical implications of dose re-distributions. In recent studies we have therefore developed an apparent diffusion coefficient (ADC) based tumour control probability (TCP) model [18–20], particularly suited for evaluation of tumour dose escalation/boosting/painting strategies.

The aim of this study was therefore to compare the use of photon- vs. proton-based RT for focal tumour boosting using biological models. More specifically we investigated the robustness of both photons and protons to inter-fractional motion, both in a tumour boost and non-boost scenario.

2. Materials and methods

2.1. Patient and image materials

The study included a cohort of seven prostate cancer patients that received RT at Aarhus University Hospital, Aarhus, Denmark (Group 1), matched to seven patients that had undergone MRI scanning including diffusion weighted imaging (DWI) prior to prostatectomy at Haukeland University Hospital, Bergen, Norway (Group 2). All patients in Group 1 had a planning CT (pCT) with delineations of all relevant volumes of interest (VOIs), as well as weekly cone beam CT (CBCT) scans during the course of RT. All patients in Group 2 had ADC maps calculated from

the DWI data, combined with MRI-based masks of the index lesion (GTV_{index}) and the whole prostate outlined for each patient [18]. We rigidly matched the patient CT data from Group 1 with patient ADC maps from Group 2 with respect to prostate volume and shape (the pairs of seven cases were selected to obtain a minimal prostate volume difference) using the MIM Maestro software (MIM Software Inc., Cleveland, Ohio) in order to obtain seven complete patient data sets consisting of CT scans, repeat CBCTs as well as rectum, bladder and GTV delineations, combined with the MRI-based GTV_{index} delineations and ADC maps.

2.2. Delineation of volumes of interest

The rectum, bladder, and gross target volume (GTV) of the prostate were delineated in all planning CT scans by a radiation oncologist. For three of the seven patients the same VOIs were delineated for their respective CBCTs. The planning target volume (PTV) was created by adding margins of 7 mm (anterior/posterior/left/right) and 9 mm (cranial/caudal) to the prostate GTV (based on VMAT procedures at our institution). The GTV_{index} contours were transferred from the delineations of the multiparametric MRI. Additionally, the normal prostate PTV, i.e. the volume of the prostate PTV outside the index lesion, was defined as the subtraction of the GTV_{index} from the PTV ($PTV_{subGTV_{index}}$).

2.3. Treatment planning

Plans with and without boost using both VMAT and IMPT were created for all seven patients using the Eclipse treatment planning system (Varian Medical Systems v13.7, Inc. Palo Alto, CA, USA). For VMAT the anisotropic analytical algorithm v13.7.14 was used, and for IMPT the proton convolution superposition algorithm v13.7.15 was used. All proton plans were coplanar, and the proton plan beam angle configuration was $90^{\circ}/270^{\circ}$ (lateral opposing beams) (Fig. 1). The PTVs for both VMAT and IMPT were prescribed to receive a mean dose of 77 Gy/35 fx, while GTV_{index} were prescribed (in the boost plans) to receive a mean dose of 95 Gy/35 fx. For all plans dose constraints, as described in Table 1, were fulfilled whenever possible.

2.4. Robustness towards inter-fractional motion

Plans with and without boost using both VMAT and IMPT were created for all seven patients using the Eclipse treatment planning

Table 1
Dose constraints and goals for rectum and PTV.

Priority	Structure	Constraint/goal
1	Rectum	$D_{1\text{cm}^3} < 74 \text{ Gy}$
1		$V_{70 \text{ Gy}} \leq 10\%$
2	PTV	$D_{95\%} \geq 73.15 \text{ Gy}$

system (Varian Medical Systems v13.7, Inc. Palo Alto, CA, USA. Dose calculations for VMAT were performed using the anisotropic analytical algorithm v13.7.14, while for IMPT the proton convolution superposition algorithm v13.7.15 was used. All proton plans were coplanar, and with a $90^\circ/270^\circ$ (lateral opposing) two-beam configuration (Fig. 1). The PTVs for both VMAT and IMPT were prescribed to receive a mean dose of 77 Gy in 35 fractions, while GTV_{index} were prescribed (in the boost plans) to receive a mean dose of 95 Gy in 35 fractions. Dose constraints, as described in Table 1, were fulfilled whenever possible for all plans.

2.5. Data analysis

Dose volume histograms (DVHs) were extracted for all plans and analysed with the tool DVHmetrics [21]. To analyse differences between VMAT and IMPT plans, several parameters were used for the organs at risk: $D_{1\text{cm}^3}$, $V_{70\text{Gy}}$ as well as the normal tissue complication probability (NTCP) for both the rectum and the bladder. We also compared PTV coverage ($D_{95\%}$) and PTV mean dose between modalities using the Wilcoxon Signed-Rank test when possible (note that PTV coverage for boost plans was evaluated separately at the PTVsubGT-V_{index} and GTV_{index} volumes). Photon-based Lyman-Kutcher-Burman NTCP models were assumed to be applicable for both protons and protons, and were used for both modalities. The rectum parameter applied ($TD_{50} = 76.9 \text{ Gy}$, $n = 0.09$, and $m = 0.13$) were for endpoint grade ≥ 2 late toxicity or rectal bleeding [22], while for the bladder ($TD_{50} = 91.0 \text{ Gy}$, $n = 0.01$, and $m = 0.19$) the endpoint was obstruction [23]. Differences in tumor control between the different treatment modalities and arms were evaluated using an ADC-based TCP model, including patient-specific tumour densities [18]. TCPs were calculated on the dose distribution of the pCT for seven patients and also for the CBCT-based re-calculations in the three patients.

3. Results

3.1. Treatment plan comparisons on the planning CT

The planned dose distributions (on the pCT) fulfilled the planning constraints for all patients, for both modalities (VMAT and IMPT) and for both arms. However, statistically significant improved PTV coverage for IMPT plans compared to VMAT was found in the boost arm (median $D_{95\%}$: 73.9 Gy vs. 73.4 Gy; $p < 0.05$). The median TCP increased from 86% (range: 59–98%) without boost to 97% (range: 96–99%) with boost ($p < 0.01$, Suppl. Fig. 1). Rectum $V_{70\text{Gy}}$ was significantly lower in the IMPT plans compared to VMAT for both arms (median: 6.4% vs. 9.3% for non-boost, and 6.4% vs. 8.1% for boost; $p < 0.05$). The rectum NTCPs were marginally lower for IMPT plans (median: 3% vs. 4% for VMAT, for both arms; $p < 0.05$). However, VMAT resulted in lower bladder NTCPs (median: 19% vs. 22% for non-boost, and 18% vs. 20% for boost; $p < 0.05$) (Table 2).

3.2. Dose re-calculations on CBCTs

In the dose re-calculations on the CBCTs, there was a small difference between IMPT and VMAT with respect to the mean dose of the PTV in the boost arm (median: 77.5 Gy (IMPT) and 76.9 Gy (VMAT)). As expected, there was a large difference between arms also when

comparing TCPs in the CBCT re-calculations, with a median of 78% (range: 59–95%) for non-boost plans, which increased to a median of 95% (range: 93–97%) for boost plans (Suppl. Fig. 2). Across the re-calculations, VMAT resulted in better high-dose sparing of the rectum for both arms, e.g. with a median $D_{1\text{cm}^3}$ of 73.6 Gy compared to 75.6 Gy for IMPT for the boost arm. Also, the bladder NTCPs were lower for VMAT across the repeat scan re-calculations for both arms; e.g. for the boost arm the median NTCP was 17% for VMAT and 20% for IMPT). No other metrics showed any significant differences between IMPT and VMAT (Table 3).

The comparison between planned distributions (on pCTs) and re-calculated distributions (on CBCTs) did not show any particular difference, for none of the modalities nor arms, except for a small difference in mean PTV dose for non-boost IMPT plans (Suppl. Table 3).

4. Discussion

In this study, we have explored the potential benefit of spot scanning PT (IMPT) compared to contemporary photon-based RT (VMAT) in a focal tumour boosting scenario for patients with prostate cancer, and in particular how robust the modalities are towards inter-fractional motion. Despite some variations, the overall finding was that the modalities performed equally well with respect to achieving the prescribed dose and coverage of the PTV and GTV_{index}. We found that the small benefit of IMPT when assessing the planned dose distributions (in the pCTs) was lost when considering the re-calculated doses.

A considerably higher TCP was found for the boost arm, for both IMPT and VMAT, compared to plans without boost. Similar results were also seen in the paper by Kuang et al. [15] and Zamboglou et al. [24] in the case of VMAT, using a different TCP model than ours. In our case, the large difference between the boost arms and non-boost arms might be due to the inclusion of tumour-index information together with ADC maps-based cell density, which increases the inter-patient tumour response differentiation, resulting in TCP curves with a larger range in $D_{50\%}$ across the cohort compared with those based on uniform cell densities [18].

Previous planning studies (not accounting for inter-fractional motion) have also compared IMPT to VMAT for focal tumour boosting [14] and sparing of normal tissues/OARs [12–14] and found a similar performance for both modalities. Furthermore, other studies have shown that PT to the prostate alone can be robust towards inter-fractional changes, which was also what was seen in our study [17,25–27]. It should be mentioned that the patients used in this study were treated with photons, i.e. the fixation and set-up methods were optimised for this modality. The robustness of IMPT might have been improved with a different and stricter patient fixation/set-up. Also, studies have shown that the robustness of proton beams change depending on the beam angles used [16,26,28]. Hence, the common practice of lateral beam angles also applied in the present study may not have been optimal in terms of robustness towards inter-fractional motion. In addition, accumulating evidence suggests that the relative biological effectiveness (RBE) of proton beams deviates from a constant factor of 1.1 as recommended by the ICRU (ICRU, 2007) but instead varies [29,30] – in particular towards the distal end of the Bragg peak of the proton beam. In turn, this could potentially influence the outcome of PT both in terms of increased RBE-weighted doses to the normal tissue and OARs, as well as higher RBE to the prostate and index lesion. Also, different beam angle configurations might make proton beams more robust towards inter-fractional changes, however, studies have shown that use of lateral beam angle configurations might influence the RBE of the proton beams to a larger degree, in particular at the locations of the OARs [31].

Early results from the FLAME trial show no difference in toxicity and quality of life between the experimental (boost) arm and the standard arm [32]. Therefore, focal boosting of prostate tumours up to 95 Gy with photon therapy seems safe. This was also what our planning study indicates for both photon therapy and PT, as there were

Table 2

Statistical analysis (Wilcoxon Signed-Rank test) results of the comparison between the pCT metrics of VMAT and IMPT (boost and non-boost cases) for all seven patients. The value in each cell is the median of the metric values for IMPT and VMAT for both arms. The bold-faced values indicate a significant difference ($p < 0.05$) in favour of IMPT, while the underlined values are in favour of VMAT.

Arm	Modality	Rectum			Bladder	PTV		Index	
		NTCP (%)	D _{1cm3} (Gy)	V _{70Gy} (%)		NTCP (%)	D _{95%} (Gy)	DMEAN (Gy)	D _{95%} (Gy)
Boost	VMAT	4	73.8	8.1	18	73.4	77.5	92.0	96.3
	IMPT	3	73.5	6.4	<u>20</u>	73.9	77.0	91.1	94.6
Non-boost	VMAT	4	73.6	9.3	<u>19</u>	73.7	77.4	–	–
	IMPT	3	73.3	6.4	<u>22</u>	73.8	76.7	–	–

Table 3

Results of the comparison between the CBCT metrics of VMAT and IMPT (boost and non-boost cases) for three patients. The value in each cell is the median of the metric values for IMPT and VMAT for both arms.

Arm	Modality	Rectum			Bladder	PTV		Index	
		NTCP (%)	D _{1cm3} (Gy)	V _{70Gy} (%)		NTCP (%)	D _{95%} (Gy)	DMEAN (Gy)	D _{95%} (Gy)
Boost	VMAT	5	74.6	8.7	17	73.0	76.9	92.3	96.3
	IMPT	5	75.6	7.8	20	73.2	77.5	92.6	96.6
Non-boost	VMAT	5	73.2	9.5	18	73.3	76.5	–	–
	IMPT	4	74.7	7.9	22	72.7	76.6	–	–

no significant differences between boost and non-boost arms in terms of normal tissue sparing. Focal boosting of the prostate may become established clinical practise, making it essential to explore the optimal treatment approach and modality for focal boosting.

One weakness of the study is the fusing of the two cohorts based on the size and volume of the prostate in each group. This was done to provide “complete” data sets in the most realistic way, instead of e.g. using randomly generated/shaped index lesions. In addition, the rigid transfer of index lesions was also done to achieve a more realistic set of placements for the lesions compared to randomly placing them in the prostate.

Another limitation of the study is the HU override in the repeat CBCTs. This was done to avoid dose calculation issues caused by the limited image quality of the CBCTs (e.g. scattering). This way we could better isolate the effects of inter-fractional motion. It should also be pointed out that the plan comparison DVH metrics used in this study were based on our departmental photon therapy protocol. The proton plans were also made without the use of robust optimisation, and also without evaluating the plans for robustness towards range uncertainties (e.g. with the tool for this in our treatment planning system); this was outside the scope of our study. From a statistical point of view, the small sample size makes it hard to draw strong conclusions, in particular on the investigations of inter-fractional motion.

In conclusion, focal tumour boosting can be delivered with either VMAT or protons, and increases the predicted TCP. There were minor differences between the two modalities, also with respect to robustness to inter-fraction motion. The small benefit of IMPT when assessing the planned dose distributions was lost when considering re-calculated doses on repeat CBCTs.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.phro.2018.06.002>.

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