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ORIGINAL ARTICLE

Evaluating the influence of organ motion during photon vs. proton therapy for locally advanced prostate cancer using biological models

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ABSTRACT

Background: Proton therapy (PT) may have a normal tissue sparing potential when co-irradiating pelvic lymph nodes in patients with locally advanced prostate cancer, but may also be more sensitive towards organ motion in the pelvis. Building upon a previous study identifying motion-robust proton beam angles for pelvic irradiation, we aimed to evaluate the influence of organ motion for PT using biological models, and to compare this with contemporary photon-based RT.

Material and methods: Eight locally advanced prostate cancer patients with a planning CT (pCT) and 8–9 repeated CT scans (rCTs) were included. Two PT plans were created, one using two lateral opposed beams at gantry angles of 90°/270° and the other using two lateral oblique beams at 35°/325°; these were compared with volumetric modulated arc therapy (VMAT) plans. All plans were optimised on the pCT and subsequently re-calculated on each rCT (following rigid alignment on the prostate). Dose distributions in organs at risk (OARs) were evaluated using mean dose, generalized equivalent uniform doses (gEUDs) and normal tissue complication probabilities (NTCPs), while mean dose and the volume receiving 98% of the dose (V98%) were used for the targets.

Results: PT significantly reduced the mean dose to the OARs and a correlation was seen in the pCTs between the prostate PTV overlapping the relevant OAR and OAR NTCPs, as was also the case for the VMAT plans. The best prostate target coverage across the rCTs for the IMPT plans were seen with two lateral opposed beams, although a poor coverage of the lymph node target was apparent based on V98% compared to the VMAT plans.

Conclusions: PT reduced the mean dose to normal tissues in the irradiation of pelvic lymph nodes and a strong association between the volume overlap and NTCPs in the pCTs were found.

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Introduction

Radiotherapy (RT) using protons has the advantage that most of the energy is deposited at a well-defined depth, leading to a lower integral dose to the patient, resulting in better sparing of the organs at risk (OARs) [1–4]. Proton therapy (PT) may therefore be beneficial for patients with locally advanced disease where regional lymph node (LN) irradiation is indicated, due to large treatment volumes. However, the well-defined range of protons makes them potentially more sensitive towards inter- and intra-fractional organ motion [5,6], such as filling of the bladder and/or rectum during the treatment course, potentially leading to degradations of the actually delivered dose distributions.

In previous studies, it was shown that inter-fractional motion induced degradations of the dose to pelvic LNs and the seminal vesicles may be difficult to resolve using either wider margins or by the choice of patient set-up alignment (Fiducial markers in the prostate vs. bony anatomy) [6]. Vargas et al. investigated the impact of prostate motion on dose coverage using PT, showing that small prostate shift (up to 5 mm) gave sufficient dose coverage while larger movements decreased the prostate dose drastically [7]. Another study of prostate-only irradiation found that the sensitivity of intensity-modulated PT (IMPT) to organ motion was strongly connected to the presence of air cavities in the rectum [8]. This study suggested overwriting the Hounsfield Units for these cavities to water or use of a rectal balloon for the purpose of increasing the robustness. Our group has recently shown that the risk of dose degradations may also be minimised through the choice of beam angles that are least sensitive to organ motion, in the setting of pelvic LN irradiation with PT [9]. In that study, the left and right sections of the LNs were irradiated with a single beam, exploring all possible gantry/couch angle combinations. Most of these PT robustness studies have analysed the influence of organ motion with respect to target coverage [10,11]. However, these uncertainties are likely to have consequences also for the doses received in the normal tissues. Furthermore, no previous study has compared the sensitivity

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Supplemental data for this article can be accessed here.

towards organ motion for pelvic irradiation with photons vs. protons in terms of biological model-based endpoints for the OARs.

The aim of this study was therefore to compare PT with contemporary photon-based RT and in particular evaluate the influence of inter-fractional organ motion for locally advanced prostate cancer, including the use of biological models.

Material and methods

Patient cohort and online volumetric imaging

The study included eight patients with locally advanced prostate cancer previously treated with intensity-modulated RT at Haukeland University Hospital, Bergen, Norway. Each patient had a planning CT (pCT) and 8–9 repeat CT (rCT) scans acquired throughout the RT course (with a slice thickness of 2-3 mm). There were no bladder/rectum filling protocols for these patients. Further details about the RT planning and delivery can be found in Muren et al. [12]. An experienced radiation oncologist delineated the prostate clinical target volume (CTV), the pelvic LN CTV (including the seminal vesicles), the bladder and the rectum in all pCTs and rCTs using the Eclipse treatment planning system (TPS) (Varian Medical Systems, Palo Alto, CA, USA). Further information on the definition of OARs and CTVs can be found in Thörnqvist et al. [13].

Treatment planning

IMPT and volumetric modulated arc therapy (VMAT) plans were created in Eclipse for the purpose of this study, using in-house clinical protocols for locally advanced prostate cancer (Supplementary Table A). The prostate planning target volume (PTV) was created from the prostate CTV by expanding the CTV 7 mm in all directions except in the superior-inferior (SI) direction, where 9 mm were used. The LN CTV was expanded by 5 mm/8 mm (SI) to create the corresponding lymph node PTV. A dose of 74 Gy in 37 fractions (74 Gy(RBE) for protons) was prescribed to the prostate PTV while a dose of 55 Gy/Gy(RBE) was prescribed to the LN PTV over the same number of fractions. All plans were approved by a senior clinical medical physicist.

Two IMPT plans were created for each patient, using two different beam configurations. One plan used the standard, two lateral opposing beam configuration (90°/270° gantry angles) while the other plan used two lateral oblique beams (35°/325° gantry angles) (Figure 1). The latter beam configuration (35°/325°) was found to be robust towards inter-fractional motion by Andersen et al. when treating the lymph nodes [9].

The VMAT plan consisted of two 15MV arcs; one arc went from 181° to 179° in a clockwise rotation, while the other went from 179° to 181° counter clockwise. To assess the influence of organ motion, all rCTs were rigidly aligned to the pCT using the isocenter of the prostate PTV in MIM (MIM Software Inc., Cleveland, OH). The two IMPT plans and the VMAT plan were then transferred to the rCTs and re-calculated.

Data analysis

All IMPT and VMAT plans (on the pCT and re-calculated on the rCTs) were evaluated using dose–volume histograms (DVHs) which were extracted from Eclipse and analysed with the tool DVHmetrics [14]. For the rectum and bladder, the mean doses were calculated along with the generalised equivalent uniform dose (gEUD) using the values 12 and 8 for the parameter a, respectively [15]. Rectum and bladder NTCPs were calculated using the Lyman–Kutcher–Burman model, with the rectum parameters reflecting grade 2 rectal bleeding [16] and the bladder parameters applying to obstruction [17] (see Table 1 for parameter details). The dose to the volume overlap between the relevant OAR and the prostate PTV was also evaluated using D2% (the dose given to 2% of the volume). The association between the NTCPs and the corresponding volume overlap ratio was evaluated by calculating the Spearman's correlation coefficient.

For the targets, the dose to the CTVs in the rCTs were investigated with the use of mean dose and V98% (the volume receiving 98% of the prescribed dose). Paired Wilcoxon signed rank tests were used to compare the two IMPT plans with VMAT (absence of normality was shown using the Kolmogorov–Smirnov test). The planned dose to the target and OARs was compared with the delivered dose in the rCTs for both modalities and all configurations.

Results

Rectum and bladder doses and NTCPs

The mean dose to the rectum in the rCTs was significantly lower for the IMPT plans with a median of 19.2 Gy for the two lateral opposed beams ($p = .014$) and 18.3 Gy for the two lateral oblique beams ($p < .01$); the VMAT plans had a median of 38.2 Gy. The same was the case for the bladder with a median of 24.8 Gy for two lateral opposed beams ($p = .014$) and 25.9 Gy for two lateral oblique beams ($p < .01$), while the VMAT plans had a median of 43.2 Gy (Figure 2 and Table 2). These patterns were overall the same as in the pCTs; the ratios between the delivered and planned mean dose ranged from 1.01 to 1.09 for the rectum and from 0.90 to 1.00 for the bladder (median values) (Table 3).

The rectum gEUDs in the rCTs were similar for both the IMPT and VMAT plans with a median in the range of 59–60 Gy for each modality ($p > .05$). However, for three patients a lower gEUD was achieved with two oblique beam plans (Figure 3). For the bladder, the gEUDs were 56 Gy (range: 50–65 Gy) for the IMPT plans and 58 Gy (range: 52–66 Gy) for the VMAT plans (Figure 3). The ratio between the pCTs and rCTs was very close to unity for both the rectum and bladder for all three modalities/beam configurations (Table 3).

The rectum NTCPs showed only modest variations in the VMAT plans across patients (range: 0.7–4%), while greater variations were seen for the IMPT plans (range: 0–13.5%) in

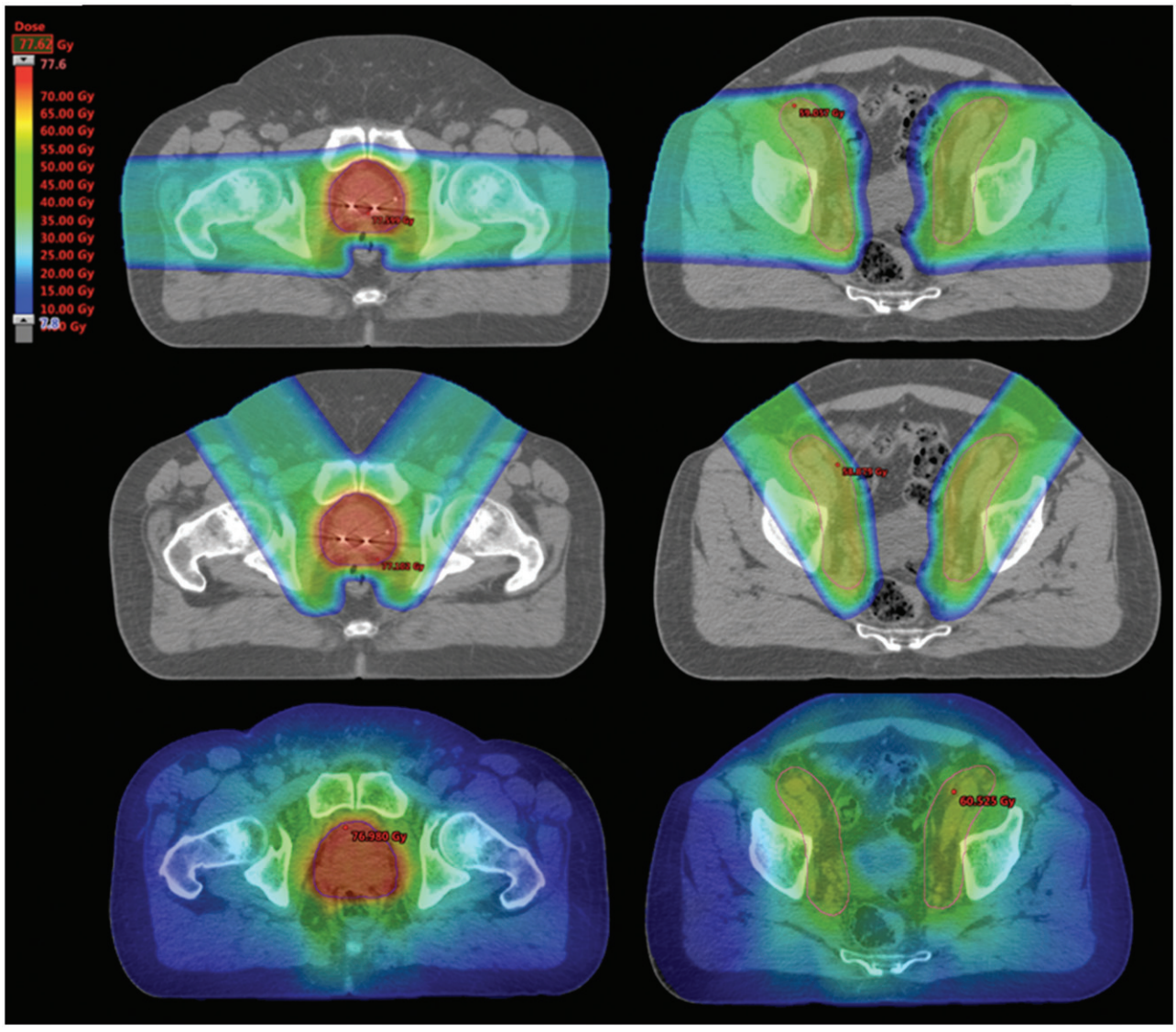

Figure 1. Dose distributions for the IMPT and VMAT plans for one patient.

Table 1. Lyman–Kutcher–Burman NTCP parameters for rectum (grade 2 rectal bleeding) [16] and bladder (obstruction) [17].

OAR	TD_{50}	n	m
Rectum	81.9 Gy	0.23	0.19
Bladder	91 Gy	0.01	0.19

the rCTs, although both modalities had a median NTCP of 1–2% (Figure 4 and Table 3).

The mean dose to the volume of the prostate PTV that overlapped with the rectum was 70–73 Gy and 73–76 Gy for D2%. No significant difference between IMPT and VMAT was seen for D2% for the overlap volume ($p > .05$). The volumetric fraction of the prostate PTV overlapping with rectum were associated with the rectum NCTPs in the pCTs for both protons and VMAT, with a Spearman's correlation coefficient above 0.9 for all three plans (Figure 5). The correlation coefficients in the rCTs were substantially lower (0.3–0.5) (Supplementary Figure 2).

For the bladder, there was no significant difference for the NTCP values between the two IMPT plans and VMAT ($p > .05$) although a large difference in range were seen; the two lateral opposed beams had a median bladder NTCP of 16% (range: 12–25%), two lateral oblique beams had a median of 17% (range: 10–31%), while VMAT had a median of 15% (range: 3–17%) (Figure 4 and Table 2). For the prostate PTV overlapping the bladder, the mean dose was 73–74 Gy and D2% was 76–78 Gy for all modalities, with no significant difference between IMPT and VMAT ($p > .05$) (Table 2). Also, for the bladder there was a linear relation between the ratio of the prostate PTV overlapping the bladder and the bladder NTCPs. The association was strongest for two lateral oblique beams (Spearman's correlation coefficient of 0.91), while the VMAT plans and IMPT plans with two lateral opposed beams had a coefficient of 0.86 and 0.74, respectively. The correlation coefficient was between 0.41 and 0.65 in the rCTs (Supplementary Figures 1 and 2).

Evaluation of target dose

There was no significant difference between the modalities for the mean dose to the prostate CTV in the rCTs ($p > .05$), however the largest variation occurred for the IMPT plans

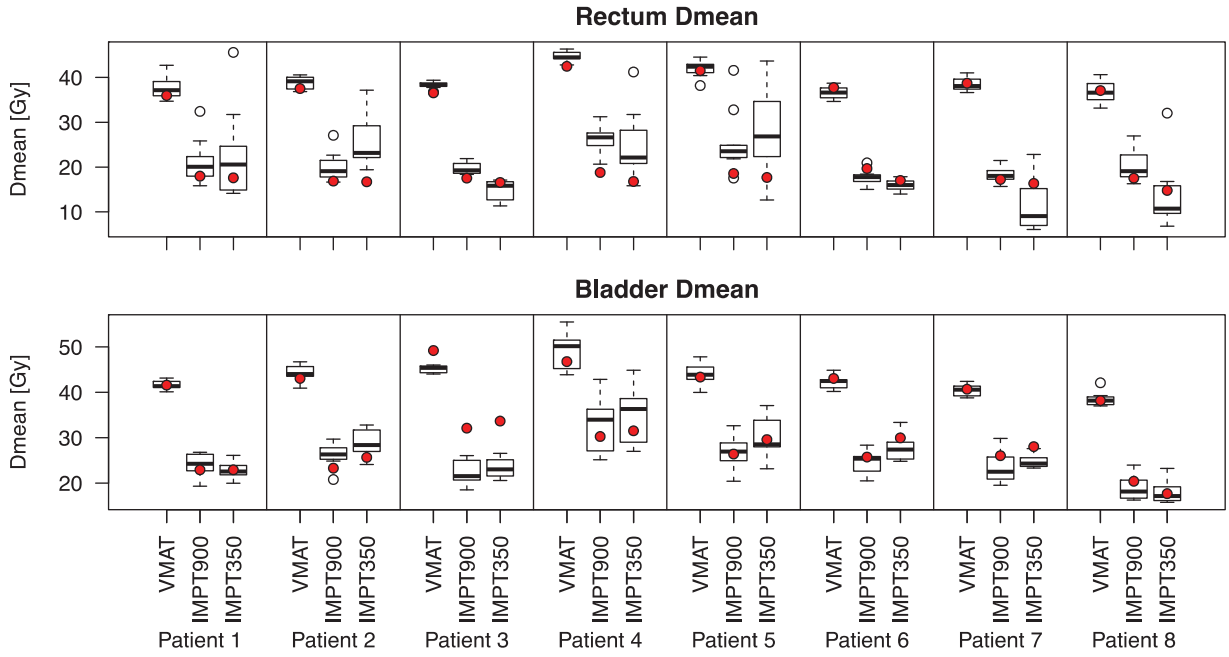

Figure 2. Mean dose for the rectum and bladder for all modalities, configurations and patients. The red dot indicates the value in the pCT, the range for the box is the 25 and 75 percentiles, with the line in the middle as the median. The upper and lower limits extend no further than 1.5 times the distance of the box.

Table 2. Median and range for different metrics and structures across patients.

Structure	Metric	VMAT	IMPT 90°/270°	IMPT 35°/325°
Rectum	Mean dose (Gy)	38.2 (33.2–46.3)	19.2 (15.0–41.6)	18.3 (6.1–41.6)
	gEUD (Gy)	59.2 (55.3–63.1)	59.6 (52.1–79.2)	59.7 (36.3–74.7)
	NTCP (%)	1.57 (0.65–3.86)	0.9 (0.2–13.5)	1.1 (0.0–12.7)
Bladder	Mean dose (Gy)	43.2 (37–55.5)	24.8 (16.3–42.9)	25.9 (15.8–44.8)
	gEUD (Gy)	58.1 (52.2–66.0)	56.3 (50.3–64.9)	56.4 (50.5–64.9)
	NTCP (%)	15.2 (2.6–17.0)	16.4 (12.3–25.1)	17.2 (9.9–30.7)
Volume overlap (Rectum)	Mean dose (Gy)	72.5 (68.1–74.0)	71.7 (63.8–78.8)	70.0 (35.7–77.2)
	D2% (Gy)	75.1 (72.3–77.4)	76.0 (70.2–93.7)	73.8 (54.0–87.1)
Volume overlap (Bladder)	Mean dose (Gy)	74.0 (69.8–75.4)	73.2 (67.5–75.4)	74.0 (68.8–78.5)
	D2% (Gy)	76.4 (74.6–77.8)	77.6 (74.5–83.0)	78.0 (72.2–85.2)
Prostate CTV	Mean dose (Gy)	73.7 (72.2–74.7)	74.0 (73.6–74.7)	73.8 (71.4–76.2)
	V98% (%)	94.4 (32.1–100.0)	94.1 (80.2–98.8)	88.9 (39.3–100)
LN CTV	Mean dose (Gy)	57.7 (56.7–60.7)	55.2 (54.5–56.0)	55.2 (53.9–55.9)
	V98% (%)	98.5 (94.2–100)	76.7 (55.6–83.2)	72.4 (50.9–94–2)

Table 3. Ratio between rCTs and pCTs for different metrics and structures across patients (range and median).

Structure	Metric	VMAT	IMPT 90°/270°	IMPT 35°/325°
Rectum	Mean dose	1.01 (0.92–1.09)	1.08 (0.89–2.11)	1.09 (0.41–2.58)
	gEUD	1.00 (0.96–1.03)	1.03 (0.92–1.33)	1.04 (0.65–1.27)
	NTCP	1.04 (0.63–1.71)	1.36 (0.48–13.17)	1.90 (0.02–14.40)
Bladder	Mean dose	1.00 (0.97–1.13)	0.96 (0.80–1.33)	0.90 (0.89–1.33)
	gEUD	1.01 (0.96–1.05)	1.00 (0.97–1.06)	1.00 (0.95–1.06)
	NTCP	1.00 (0.89–1.00)	1.05 (0.99–1.44)	1.11 (0.76–1.77)
Volume overlap (Rectum)	Mean dose	1.00 (0.94–1.01)	1.01 (0.90–1.10)	0.98 (0.50–1.08)
	D2%	1.00 (0.98–1.02)	1.05 (0.98–1.29)	1.02 (0.75–1.19)
Volume overlap (Bladder)	Mean dose	1.00 (0.95–1.01)	0.98 (0.93–1.00)	1.00 (0.94–1.05)
	D2%	1.00 (0.99–1.00)	1.01 (1.00–1.07)	1.02 (0.97–1.10)
Prostate CTV	Mean dose	1.00 (0.98–1.01)	1.00 (1.00–1.01)	1.00 (1.00–1.03)
	V98%	1.00 (0.40–1.00)	0.95 (0.86–0.99)	0.90 (0.42–1.00)
LN CTV	Mean dose	1.00 (1.00–1.01)	1.00 (1.00–1.01)	1.00 (0.98–1.00)
	V98%	1.00 (0.96–1.00)	1.00 (0.94–1.00)	1.00 (0.83–0.99)

with two lateral oblique beams (range: 71.4–76.2 Gy), while two lateral opposed beams had the smallest variation (range: 73.6–74.7 Gy) (Supplementary Figure 3). The same trend was seen for V98% ($p > .05$), where the two lateral opposed beams plan had the smallest range (range: 80–99%), while the plans with two lateral oblique beams and the VMAT plans had a larger range (range: 39–100% and 32–100%, respectively) (Supplementary Figure 4).

The mean dose to the LN CTV in the rCTs was 53.9 Gy (98% of the prescribed dose of 55 Gy to the LNs) or above for all scans and modalities; although the VMAT plans had the best coverage with a dose range of 56.7–60.7 Gy

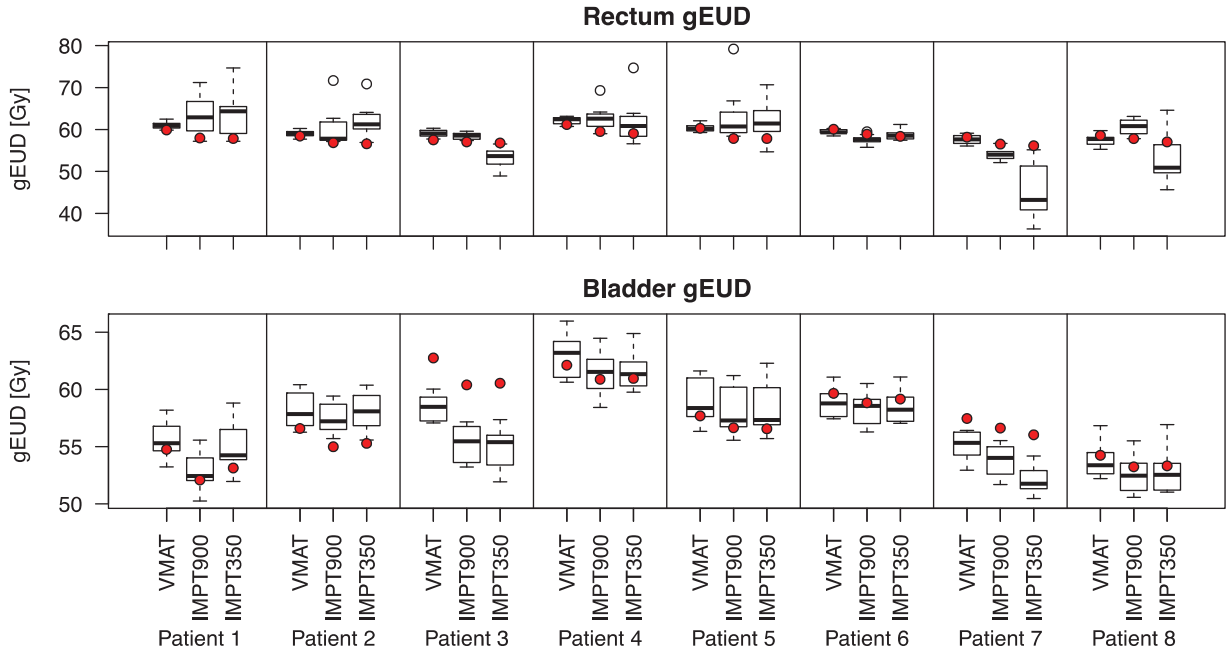

Figure 3. gEUD values for the rectum and bladder for all modalities, configurations and patients. The red dot indicates the value in the pCT, the range for the box is the 25 and 75 percentiles, with the line in the middle as the median. The upper and lower limits extend no further than 1.5 times the distance of the box.

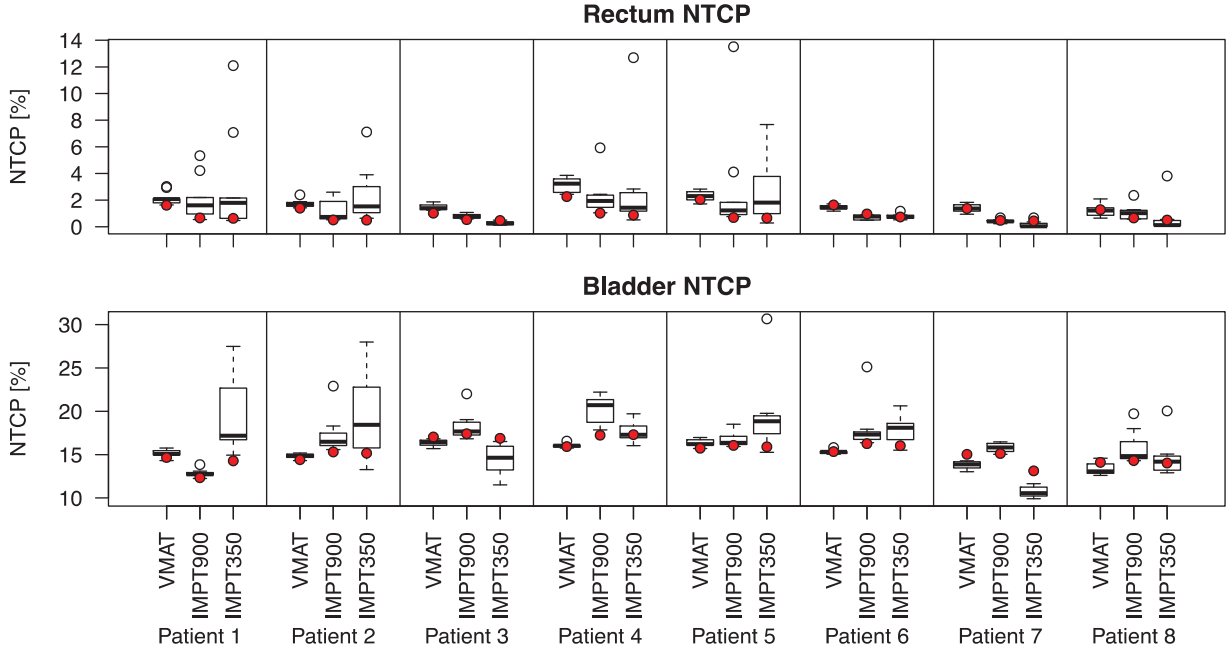

Figure 4. NTCP values for the rectum and the bladder for all modalities, configurations and patients. The red dot indicates the value in the pCT. The range for the box is the 25 and 75 percentiles, with the line in the middle as the median. The upper and lower limits extend no further than 1.5 times the distance of the box.

(Supplementary Figure 3). For V98% a low target coverage was seen for the IMPT plans with a median of 76.7% for two lateral opposed beams and 72.4% for two lateral oblique beams while the VMAT plans had a median of 98.5% (Table 3 and Supplementary Figure 4).

Discussion

In this study, we have evaluated the potential benefit of IMPT compared with VMAT in a group of patients with locally advanced prostate cancer when taking inter-fractional organ motion into account, and in particular used biological model endpoints in the analysis. The main finding was that IMPT can reduce the mean dose to the OARs also when taking organ motion into account. However, in the high-dose regions, the doses to the rectum and bladder were comparable with the doses using VMAT, which resulted in the gEUD and NTCP values to be overall similar for the two modalities. We also found strong associations between the fraction of the prostate PTV overlapping with the rectum/bladder and the respective NTCPs for these two organs.

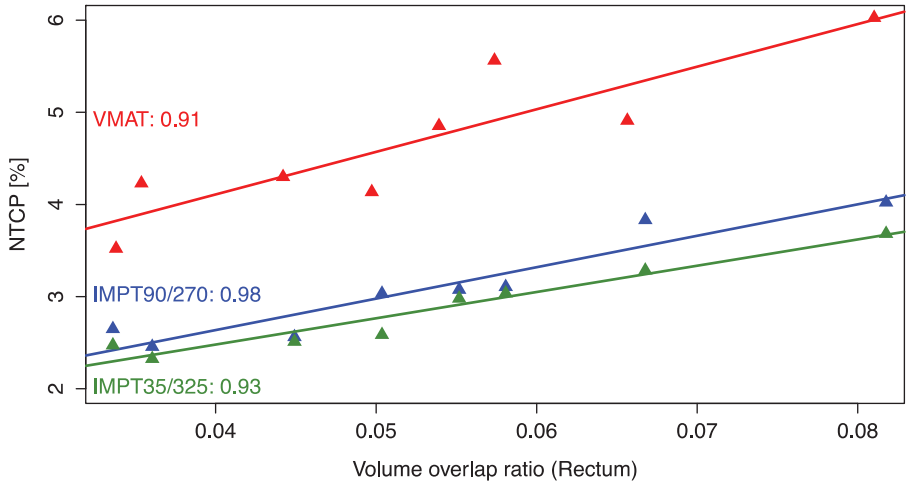

Figure 5. Volume overlap ratio vs. rectum NTCP values in the pCTs for all patients. The solid lines are the linear regression curves fitted to the data and next to the labels are Spearman's correlation coefficient indicated.

Securing sufficient target coverage is the primary concern in radiotherapy. Our plans showed that VMAT gave the best target coverage for the LN CTV across all patients and scans. However, a good target coverage of the prostate CTV was achieved using both VMAT and two lateral IMPT beams, although the latter gave the best results overall with regards to achieving the prescribed dose and coverage of the target. In a previous study from our group, Andersen et al. [9] found the lateral angles to be less robust due to density changes, while two lateral oblique beams were more robust. It should be pointed out that in this previous study, each lateral section of the LNs was targeted separately without irradiating the prostate (with single beam plans), and also a different TPS was used.

Two lateral opposed beams may not be suitable if there are very large variations in the rectum or bladder during the treatment course. This was studied by Thörnqvist et al. [6], where an additional margin (up to 10 mm) was not sufficient to fully account for the dose degradation in the seminal vesicles and LNs. However, they did find the prostate target to be robust when fiducial marker-based positioning was used. In our study, we found poor target coverage of the LN CTV for V98%, however the ratio between the delivered and planned dose were close to unity. We also found the prostate target to be robust when using VMAT and two lateral opposed beams. The latter have the disadvantage that the dose to the femoral heads increases, when compared with photon-based RT [18]. However, Valery et al. recently reported no increase in the risk of hip fracture nor hip pain when treating prostate cancer patients with PT [19].

In our study the mean dose to the rectum and bladder were significantly lower when using PT, however, a different trend was seen for the NTCP values where they were similar or higher, which also was the case for the gEUD values. The proton dose distribution had areas with doses above 70 Gy in the OARs increasing the gEUDs and NTCP values, which is due to overlap between the OARs and the PTVs. The NTCP values, especially for the rectum, were in general low across modalities, however the parameters chosen are only assessing selected endpoints. There might be low dose dependent toxicity, which is not accounted for in the chosen model. According to QUANTEC, doses above 70 Gy for the rectum are more consistently associated with toxicity, while for the bladder the dose/volume tolerance levels are less established [20,21]. Other studies have also showed that PT spares the rectum and bladder in the low dose range, however at higher doses PT becomes somewhat comparable with photons. Zhang et al. [22] compared PT with intensity-modulated RT (IMRT) for patients with early-stage prostate cancer and found a better sparing of the rectum at low doses for IMPT, while at doses higher than 50 Gy IMRT was better at sparing the rectum. For the bladder, at doses lower than 50 Gy, PT was superior, however at doses higher than 50 Gy, IMRT and PT showed similar sparing. Trofimov et al. [23] compared IMRT with IMPT for early-stage prostate cancer, showing that PT was better at sparing the rectum and bladder in the low dose region, while IMRT was better at sparing the OARs at high-dose regions. In another study, Rana et al. [18] compared IMPT with VMAT for high-risk prostate cancer and showed that PT reduced the dose in the low and medium dose range for the bladder, whereas VMAT was superior at reducing the dose in the high-dose region.

Other studies have investigated the use for PT at different pelvic sites. Lin et al. [24] compared PT with IMRT for whole pelvic irradiation in women with gynaecologic cancer. They observed a sparing of the OARs in low-dose regions using PT and a robust target coverage relative to setup uncertainties. van de Schoot et al. [25] compared IMPT with VMAT using image-guided adaptation in cervical cancer to accommodate inter-fractional changes and found PT to maintain adequate target coverage while reducing the dose to the OARs significantly. Blanco Kiely et al. [26] compared proton pencil beam scanning (PBS) with VMAT in locally advanced rectal cancer and found PBS to be robust against inter-fractional changes and concluded that PBS may decrease toxicity by reducing the OAR dose. These studies indicate that PT should be considered for irradiation of the pelvis also for other tumour sites than the prostate.

In our study, target dose degradation occurred for some of the IMPT plans, most likely due to inter-fractional motion.

The study by van de Schoot et al. [25] used adaptation as a tool to accommodate anatomical changes in cervical cancer patients and maintained a good target coverage. Internal organ motion during treatment can also lower the dose to the targets and increase the dose to the OARs. For this purpose, rectal balloons and/or spacers can be considered. Teh et al. [27] found the use of a rectal balloon to significantly reduce prostate motion during IMRT, which also reduced the rectal volume receiving a high dose, however they only irradiated the prostate. This was also seen by Wachter et al. [28]. Further studies are needed to investigate the robustness of IMPT when combined with the use of rectal balloons and/or spacers, potentially leading to lower rectum doses while maintaining target dose coverage.

In conclusion, two lateral opposed beams can be used when treating locally advanced prostate cancer with PT. This field configuration gave the best dose coverage of the prostate CTV and covered the LN CTV sufficiently based on the mean dose. PT gave a significantly lower mean dose to the OARs, however the gEUD and NTCP values were similar to those for the VMAT plans due to the overlap volume between the OARs and prostate PTV. Strong associations were found between the fraction of the PTV overlapping with the rectum and bladder and the corresponding NTCP values for both of these organs.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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