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Short communications and technical notes

The impact of bladder preparation protocols on post treatment toxicity in radiotherapy for localised prostate cancer patients

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ABSTRACT

Objective: This study compares the post radiotherapy related toxicity between the use of an empty and a full bladder preparation protocol in patients receiving radical radiotherapy for localised prostate cancer.
Methods and materials: A retrospective review of patient treatment records in which they were treated with a standard radiotherapy schedule (60Gy/20 fractions) to prostates and base of seminal vesicles only and followed two different bladder preparation (empty and full) protocols was carried out. This included each patient's daily image guided radiotherapy (IGRT) setup, treatment time, bladder size on planning computed tomography, organs at risk dose volume histograms (OAR DVHs) and 12 months post treatment gastrointestinal (GI) and genitourinary (GU) toxicity data.
Results: 20 patients were included. There were significant differences in IGRT setup between the two groups. Although treatment times of the two groups were not significantly different, 5/200 (2.5%) sessions were longer than 20 min in the full bladder group while this was not found in the other group. Associations between bladder preparation protocols and GI ($p = 1.0$) and GU ($p = 0.6$) toxicities were not statistically significant. The bladder size on planning CT was not significantly correlated to the GI ($R = 0.06$, $p = 0.8$) or GU ($R = 0.27$, $p = 0.3$) toxicity scores. No significant differences were found in OAR DVHs between patients with and without GI and GU toxicities. No grade 3/4 toxicities were reported.
Conclusion: The empty bladder preparation approach has non-inferior acute and intermediate post RT GI and GU toxicities in patients treated for localised prostate cancer with advanced radiotherapy techniques compared to the full bladder preparation.

Background

Radiotherapy (RT) is one of the most important components in radical prostate cancer management [1]. Conventionally treatment is planned with the bladder full based on the principle that this will result in better sparing of bladder and small bowel. In the last decade, there have been progressive developments in the radiation delivery techniques. The use of intensity and volumetric modulated radiotherapy (IMRT and VMAT) allows individualized highly conformal dose delivery to the prostate while sparing the surrounding normal tissue. The use of such advanced techniques in external beam RT to prostate only enables dose reduction to organs at risk (OARs) and in this setting a full bladder preparation has less influence [2].

Not uncommonly, either because of advanced age or irritating urinary symptoms, prostate cancer patients find it difficult to maintain a full bladder during radiotherapy. Empty-bladder treatment has therefore been advocated in patients who require RT to the prostate alone. This approach provides better patient comfort and potentially better reproducibility. This study assesses the impact of an empty bladder protocol in patients receiving radical RT to the prostate in terms of acute and intermediate post RT related toxicities.

Methods and materials

Twenty patients with baseline International prostate symptom scores (IPSS) less than 7 treated for localised prostate cancer between October 2014 and March 2015 were included, All patients were stage T2N0M0 with Gleason scores <=7. Three fiducials markers are implanted 7 to 10 days prior to the planning CT appointments. Any patients who required RT to nodal area were excluded in this study.

RT planning and treatment were performed with the patient in a supine position with a knee rest. CT slices were obtained at 3 mm

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intervals. The patients received verbal advice on bladder preparation at their CT planning appointments. For the full bladder preparation protocol, the advice was to void the bowel and bladder and then drink 300 ml of water within the next 15 min and 30 min later proceed with the RT planning scan. This process would then be repeated daily prior to each treatment. For the empty bladder preparation protocol, patients were asked to empty bowel and bladder once at the radiotherapy department immediately before planning CT and treatments.

Target and OARs including the bladder and rectum were delineated by the attending radiation oncologist on the Varian Eclipse treatment planning system (Varian Medical Systems, Inc., Palo Alto, CA). VMAT was delivered using a 6 MV accelerator treating the prostate and base of seminal vesicles to 60 Gy in 20 fractions with a 10 mm planning target volume (PTV) margin, except posteriorly where 5 mm was used. All patients included in the study were planned under the same departmental clinical protocol with VMAT using PTV and OAR dose constraints as shown in Table 1. Daily online IGRT corrections using kV planar imaging matching to fiducials were used for all patients.

A retrospective review of treatment records of patients who followed the two different bladder preparation (empty and full) protocols was carried out. This included daily online image guided radiotherapy setup data, treatment duration, bladder size on planning computed tomography, PTV and OARs dose volume histogram (DVH) data and post treatment follow up data.

The daily online IGRT setup data were defined as the absolute vertical (VRT), longitudinal (LNG) and lateral (LAT) couch shifts required for each treatment fraction. The population systematic and random setup errors for both groups of patients were calculated according to the On-target report [3]. The treatment time for each fraction was calculated as the time difference between the starts of first imaging field and the last treatment field. Mann Whitney U tests were used to explore differences in OARs dose volume histogram (DVH) data, setup data and treatment times between the two bladder preparation protocols.

The follow up data was collected prospectively and included 12 months post treatment gastrointestinal (GI) and genitourinary (GU) toxicity scoring using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 protocol which is routinely collected prospectively during and after radiotherapy. Fisher's exact test was performed for significant associations between acute GI and GU toxicities and bladder preparation protocols. The Spearman's Rank Correlation Coefficient was used to establish the strength of the relationship between the bladder size on planning CT and the toxicities.

Results

20 patients (10 for each bladder preparation protocol) undergoing 400 treatment sessions were included in the study with a median follow up time of 14 months. The treatment record data are summarised in Table 2.

As shown in Table 2, there were statistically significant differences in the absolute couch shifts required for the daily IGRT in both VRT and LNG between the two groups of patients. The larger population systematic and random setup errors in the full bladder group might be due to larger variations in bladder size.

Despite the fact that the treatment times of the two groups are not significantly different ($p = 0.5$), Five treatment sessions in 1

Table 1
PTV, rectum and bladder DVH data for the two bladder filling protocols.

Volume	Dose objectives	Tolerance	Empty bladder protocols Mean (95%CI)	Full bladder protocols Mean (95%CI)	P-value
PTV	D98%	≥57 Gy	58.0 Gy (57.8 Gy–58.3 Gy)	57.9 Gy (57.7 Gy–58.0 Gy)	p = 0.32
	D50%	=60 Gy	60 Gy	60 Gy	N/A
	D2%	≤63 Gy	61.6 Gy (61.4 Gy–61.8 Gy)	61.6 Gy (61.5 Gy–61.7 Gy)	p = 0.74
Rectum	V42Gy	60%	30.2% (22.7–37.7%)	30.6% (21.0–40.2%)	p = 0.85
	V50Gy	50%	19.0% (14.8–23.2%)	18.7% (11.4–25.9%)	p = 0.44
	V54Gy	30%	14.2% (11.0–17.3%)	13.6% (7.5–19.6%)	p = 0.28
	V58Gy	15%	7.9% (6.0–9.9%)	7.9% (3.9–11.9%)	p = 0.44
Bladder	V42Gy	50%	53.1% (43.9–62.3%)	19.8% (13.9–25.7%)	p < 0.05
	V50Gy	25%	40.0% (33.0–47.1%)	14.1% (10.5–17.7%)	p < 0.05
	V62Gy	5%	0.5% (0.2–1.1%)	0.2% (0.1–0.4%)	p = 0.22

Table 2
Summarise the treatment record data for the two bladder filling protocols.

		Empty bladder protocols		Full bladder protocols		P-value
Age Mean (range)		76 years old (66–80)		75 years old (68–81)		N/A
Bladder size on planning CT Mean (95%CI)		63 cc (51.9–74.4)		265 cc (200.5–328.6)		p < 0.05
*Maximum GI toxicity scores at 12 months post RT		Grade 0	Grade 1/2	Grade 0	Grade 1/2	p = 1.00
		7/10 (70%)	3/10 (30%)	8/10 (80%)	2/10 (20%)	
*Maximum GU toxicity scores at 12 months post RT		Grade 0	Grade 1/2	Grade 0	Grade 1/2	p = 0.60
		4/10 (40%)	6/10 (60%)	2/10 (20%)	8/10 (80%)	
Treatment time for each fraction Mean (95%CI)		5.8 min (5.1–6.5)		6.2 min (5.3–7.1)		p = 0.50
IGRT corrections Mean (95%CI)	VRT	3.2 mm (2.8–3.5)		4.1 mm (3.6–4.6)		p < 0.05
	LNG	2.6 mm (2.3–2.8)		3.5 mm (2.9–4.0)		p < 0.05
	LAT	2.8 mm (2.5–3.0)		2.5 mm (2.2–2.8)		p = 0.13
Population systematic error	VRT	2.8 mm		4.3 mm		N/A
	LNG	2.1 mm		3.2 mm		
	LAT	2.9 mm		3.0 mm		
Population random error	VRT	2.8 mm		2.9 mm		N/A
	LNG	2.5 mm		3.2 mm		
	LAT	2.4 mm		2.4 mm		

* There were no grade 3 or 4 toxicities.

Table 3
Summarise the rectum and bladder DVH data for the patients with and without GI and GU toxicities.

OAR	Dose objectives	GI grade 0 (15/20) Mean (95%CI)	GI grade1/2 (5/20) Mean (95%CI)	P-value
Rectum	V42Gy	30.2% (24.0–36.5%)	30.9% (13.4–48.5%)	p = 1.00
	V50Gy	18.5% (14.5–22.5%)	19.7% (5.6–33.8%)	p = 0.93
	V54Gy	13.5% (10.3–16.6%)	15.1% (3.5–26.6%)	p = 0.93
	V58Gy	7.6% (5.5–9.7%)	8.9% (1.6–16.2%)	p = 0.80
OAR	Dose objectives	GU grade 0 (6/20) Mean (95%CI)	GU grade1/2 (14/20) Mean (95%CI)	P-value
Bladder	V42Gy	38.4% (26.5–50.4%)	30.6% (11.9–49.4%)	p = 0.17
	V50Gy	28.5% (19.3–37.7%)	22.7% (9.1–36.4%)	p = 0.10
	V62Gy	0.3% (0.1–0.7%)	0.1% (0.0–0.2%)	p = 0.14

patient were longer than 20 min in the full bladder group while this was not found in the empty bladder protocol group.

There were no grade 3 or 4 toxicities reported for all patients. The associations between bladder preparation protocols and GI ($p = 1.0$) and GU ($p = 0.6$) toxicities are not statistically significant despite the fact that significant differences ($p < 0.05$) were found in bladder size on planning CT between the two protocols. The bladder size on planning CT is not significantly correlated to the GI ($R = 0.06$, $p = 0.8$) or GU ($R = 0.27$, $p = 0.3$) toxicity scores.

As illustrated in Table 1, all plans from both bladder preparation protocols achieved all PTV and rectum dose objectives, and the V62Gy objective for bladder. There are statistically significant differences found in V42Gy and V50Gy of bladder between the two bladder preparation protocols. Reviewing plans in the empty bladder group, 8/10 and 9/10 failed to achieve the V42Gy and V50Gy dose objectives while all plans in the full bladder group managed to be within tolerance.

No statistically significant differences were found in any dose objectives between patients with grade 0 and grade 1/2 GI and GU toxicities respectively as shown in Table 3.

Discussion

Quality of life (QOL) is an important factor to be considered in prostate cancer management. RT induced GI and GU morbidities play a major role in the post-treatment QOL in prostate external beam RT [4]. The present study aimed at investigating the impact of bladder preparation protocols on post RT GI and GU toxicities in patients receiving state of the art RT to the prostate and base of seminal vesicles only. Our post RT follow-up results show an excellent outcome in terms of post RT toxicities at 12 months with IMRT and VMAT and this is comparable with findings from other studies [2,5–7].

This advanced RT delivery not only enables a more conformal delivery of radiation to the target, but also a steep dose gradient fall off to minimise doses to OARs specifically for sparing the rectum and bladder. Thus the advantages of full bladder treatment are less compelling and this is supported by our results of a weak correlation between the bladder size on planning CT and the GI toxicity scores and no significant differences in rectum DVH data between the GI grade 0 and grade 1/2 patients as suggested in Table 1.

Similarly the bladder complication rates within our cohort are low in both empty and full bladder groups. This is in line with the findings from Mullaney et al. suggesting that no statistically significant correlations were found between bladder preparation protocols and GI/GU toxicities [8].

As suggested by the CHHiP trial, the bladder dose constraints for the 60 Gy treatment arm are V40.2Gy (68% of the prescribed dose) <50%, V48.6Gy (81% of the prescribed dose) <25% and V60Gy (100% of the prescribed dose) <5% [9]. These are comparable with our departmental bladder dose objectives used in the study. The doses to the bladder in a prostate radiotherapy plan are expected to be higher as a percentage when an empty bladder preparation protocol is used. As expected, the majority plans in the empty bladder group failed to achieve the V42Gy and V50Gy bladder dose objectives while all plans in the full bladder group achieved these two dose objectives. However, the GU toxicities at 12 months were not statistically significant between two bladder preparation protocols in our study. It implies that the V42Gy and V50Gy bladder dose objectives may not be the best predictor for post RT GU toxicities in the cohort of patients receiving RT to their prostates and base of seminal vesicles only. This statement is further supported by our findings in Table 3 that there were no significant differences in these two bladder dose objectives between the GU grade 0 and grade 1/2 patients.

There is a common problem that patients are unable to maintain consistent full bladder volume during planning and treatments [10]. It has been shown that the bladder size obtained from a static planning CT scan usually does not represent the actual bladder volume being treated during a course of fractionated radiotherapy [11]. As illustrated in Table 2, the extent of daily IGRT corrections required for patients in the full bladder group was higher than the empty bladder group. The larger population systematic and random setup errors in the full bladder group might be due to inconsistent bladder filling and patients' discomfort of holding a full bladder for RT [12]. This large variability in bladder volume during RT as reported by other researchers might contribute to the lack of robust and reliable bladder dose volume constraints for prostate external beam RT [11,13].

Although no significant differences were found in treatment times between the two bladder filling protocols as suggested in Table 2, it's expected that patients in the full bladder group would need to spend a longer time in the RT department per treatment session. Patients in the full bladder group were sent off to refill their bladders if setup could not be reproduced from the planning CT images; in practice one patient in particular had to repeatedly do this with 5 of his 20 treatment sessions being longer than 20 min. With similar post RT toxicities in the empty bladder group, this approach will give better patient comfort and minimise the length of each treatment session.

It is acknowledged that the obvious limitations of our study are its retrospective nature and the relatively small number of patients included. With the low number of episodes of grade 1/2 GI and GU toxicities, variations in the post RT GI and GU toxicities at 12 months between two bladder preparation protocols can be due to different patient sensitivities to RT. Late toxicities will have greatest impact on quality of life and longer follow-up and it is therefore important to validate this approach, in particular to assess whether the difference in low dose volumes to the bladder has any impact on outcome.

Conclusion

Compared with full bladder preparation, this study suggests that the empty bladder preparation protocol has non-inferior acute and intermediate post RT GI and GU toxicities in localised prostate patients receiving advanced radiotherapy treatment techniques to prostates and base of seminal vesicles only. This empty bladder approach can provide better patient comfort and reproducibility during the whole treatment course. A larger cohort of patients with longer follow up will be required to prove that insignificant variations in GI and GU toxicities are caused by different bladder preparation protocols.

Conflict of interest

The authors declared that there is no conflict of interest.

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