Toxicity after post-prostatectomy image-guided intensity-modulated radiotherapy using Australian guidelines

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Abstract

Introduction: We evaluated single institution toxicity outcomes after post-prostatectomy radiotherapy (PPRT) via image-guided intensity-modulated radiation therapy (IG-IMRT) with implanted fiducial markers following national eviQ guidelines, for which late toxicity outcomes have not been published.

Methods: Prospectively collected toxicity data were retrospectively reviewed for 293 men who underwent 64–66 Gy IG-IMRT to the prostate bed between 2007 and 2015.

Results: Median follow-up after PPRT was 39 months. Baseline grade ≥2 genitourinary (GU), gastrointestinal (GI) and sexual toxicities were 20.5%, 2.7% and 43.7%, respectively, reflecting ongoing toxicity after radical prostatectomy. Incidence of new (compared to baseline) acute grade ≥2 GU and GI toxicity was 5.8% and 10.6%, respectively. New late grade ≥2 GU, GI and sexual toxicity occurred in 19.1%, 4.7% and 20.2%, respectively. However, many patients also experienced improvements in toxicities. For this reason, prevalence of grade ≥2 GU, GI and sexual toxicities 4 years after PPRT was similar to or lower than baseline (21.7%, 2.6% and 17.4%, respectively). There were no grade ≥4 toxicities.

Conclusions: Post-prostatectomy IG-IMRT using Australian contouring guidelines appears to have tolerable acute and late toxicity. The 4-year prevalence of grade ≥2 GU and GI toxicity was virtually unchanged compared to baseline, and sexual toxicity improved over baseline. This should reassure radiation oncologists following these guidelines. Late toxicity rates of surgery and PPRT are higher than following definitive IG-IMRT, and this should be taken into account if patients are considering surgery and likely to require PPRT.

Key words: adjuvant radiotherapy; image-guided radiation therapy; prostate cancer; salvage therapy; toxicity.

Introduction

Radical prostatectomy is the predominant form of treatment for prostate cancer in Australia, with guidelines recommending consideration of adjuvant radiotherapy (ART) after prostatectomy for high-risk features thought to be predictors of residual local disease to reduce biochemical and local recurrence and clinical progression.1–3

Use and recommendation for ART in patients with high-risk pathology after prostatectomy has been 15% or less in multiple population studies, despite evidence of a survival benefit in the Southwest Oncology Group trial.4–7 Along with concerns over treatment, inconvenience and cost, toxicity may be one of the major concerns limiting use of ART, with genitourinary (GU) grade 2–3 toxicity greater than 20% in multiple series using conventional or 3D conformal radiotherapy (RT).8–10 In the post-prostatectomy setting, however, patients often experience toxicity prior to commencing radiotherapy, and hence comparison against baseline is important. Despite this, published details of toxicity evaluation in comparison to baseline are often missing. Use of image-
guided intensity-modulated radiotherapy (IG-IMRT) may reduce toxicity, with a recent series reporting low levels of new acute and late toxicity rates with IG-IMRT, although other series using IMRT report GU grade 2–3 toxicity rates of approximately 20% without stating whether these are new compared to baseline. Understanding patterns and rates of treatment toxicity before, during and after post-prostatectomy radiotherapy (PPRT) is important in counselling patients and referring doctors regarding its benefits and risks.

There is limited published literature reporting Australian outcomes after PPRT with limited follow-up and small numbers from series using older radiotherapy techniques. The Australian eviQ guidelines (www.eviQ.org.au, Cancer Institute NSW) for PPRT were formulated in 2007, with the contouring guidelines based on those developed by the Australian Faculty of Radiation Oncology Genito-Urinary Group (FROGG) in 2006. These evidence-based contouring guidelines had not been in routine use prior to the consensus process, and although some reports exist describing acute toxicity outcomes, there have been no published late toxicity outcomes. While implanted fiducial markers have been shown to improve matching compared to using surgical clips, there are also no published long-term toxicity reports using them for image-guided PPRT.

The objective of this evaluation is to review prospectively collected acute and late toxicity outcomes in a consecutive series of patients treated with post-prostatectomy IG-IMRT with implanted fiducial markers, using the Australian eviQ and FROGG consensus guidelines.

**Methods**

**Patient cohort**

The electronic medical record (EMR) was assessed to identify patients treated with PPRT to the prostate bed between 2007 and 2015. Patients were treated by a single radiation oncologist utilising the eviQ guidelines for contouring. Patients were excluded if they had macroscopic recurrence, pathologically or clinically involved pelvic lymph nodes or metastatic disease. Patients were considered as being treated with adjuvant intent if PPRT was commenced due to high-risk pathological features and post-operative PSA was ≤0.1, and salvage intent for a rising PSA or a post-operative PSA >0.1. The database was closed to analysis in September 2016. The institutional Human Research Ethics Committee classified the evaluation as a quality assurance project.

**Treatment**

Simulation, planning and treatment techniques have been previously discussed. Transrectal ultrasound-guided inserted gold fiducial markers and IV contrast were used unless contraindicated, with planning MRI fused to aid volume delineation. Patients were treated with leuprorelin or goserelin neoadjuvant ± adjuvant androgen deprivation therapy (ADT) according to clinician discretion (utilising eviQ recommendations as a guide), patient choice and/or due to expected delay in RT due to recovery of urinary function.

**Follow-up and toxicity**

A retrospective review was performed of baseline, on treatment and follow-up toxicity prospectively scored by radiation oncologists and radiation oncology registrars in the Mosaic (Elekta, Stockholm, Sweden) EMR using version 4 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scoring criteria. Version 3 was used prior to July 2011, and this was recoded into version 4 for analysis. Urinary urgency was introduced in version 4 and had less toxicity scores available. RT nurses and radiation therapists also performed on-treatment assessments. Patients who were lost to follow-up were invited to attend clinic or participate in telephone follow-up.

Toxicity evaluation was performed at 3 months follow-up after radiotherapy and at least every 12 months up until 5 years, then at 7 and 10 years. Baseline toxicity was scored prior to commencement of ADT or radiotherapy. Acute toxicity was defined as occurring during or within 90 days after radiotherapy. Late toxicity was from 90 days after completion of radiotherapy and grouped by dates falling within 6 months of the corresponding time period. If multiple scores were obtained, the highest score was used. New toxicity was defined as a toxicity score greater than baseline score for each toxicity item. If no baseline or follow-up toxicity was scored for a particular item, it was not used for calculation of new toxicity. Change in individual toxicity grade from baseline to 4 years after PPRT was categorised according to whether the scores improved, did not change or worsened.

**Statistical methods**

Descriptive statistics was used for baseline, acute and late toxicity. Toxicity prevalence was calculated according to the number of patients with data available at the relevant time point. Kaplan–Meier analysis was performed for any late grade ≥2 toxicity by category according to radiotherapy intent, with Cox proportional hazards regression model used to assess the effect of intent, age ≥65 years, baseline grade ≥2 toxicity, acute grade ≥2 toxicity and use of ADT on late grade ≥2 toxicity. Data collection and analysis were performed using SPSS v23 (IBM Corporation, Armonk, NY, USA).

**Results**

A total of 293 men were treated with post-prostatectomy IG-IMRT to the prostate bed with median follow-up of
Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjuvant (n = 57)</th>
<th>Salvage (n = 236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up from RT/ADT (range)</td>
<td>40 months (3–85)</td>
<td>37 months (0–98)</td>
</tr>
<tr>
<td>Median duration from surgery to RT/ADT (range)</td>
<td>4 months (1–14)</td>
<td>20 months (1–185)</td>
</tr>
<tr>
<td>Age at radiotherapy, median (range)</td>
<td>63 (48–75)</td>
<td>66 (49–78)</td>
</tr>
<tr>
<td>Age at prostatectomy, median (range)</td>
<td>63 (48–75)</td>
<td>64 (47–76)</td>
</tr>
<tr>
<td>Pre-operative PSA (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.7 (1.1–61)</td>
<td>7.8 (1.2–33)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>10 (18%)</td>
<td>62 (26%)</td>
</tr>
<tr>
<td>10–20</td>
<td>45 (79%)</td>
<td>164 (69%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>2 (4%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Unavailable</td>
<td>0</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Lymph node dissection/ sampling performed</td>
<td>41 (72%)</td>
<td>156 (66%)</td>
</tr>
<tr>
<td>Pathological T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥7</td>
<td>9 (39%)</td>
<td>77 (33%)</td>
</tr>
<tr>
<td>≤6</td>
<td>1 (2%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>≥8</td>
<td>14 (25%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>&lt;8</td>
<td>34 (62%)</td>
<td>129 (54%)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>37 (65%)</td>
<td>113 (48%)</td>
</tr>
<tr>
<td>EPE</td>
<td>44 (77%)</td>
<td>125 (53%)</td>
</tr>
<tr>
<td>SVI</td>
<td>21 (37%)</td>
<td>41 (17%)</td>
</tr>
</tbody>
</table>

Table 2. Baseline, acute and late toxicity by genitourinary (GU), gastrointestinal (GI) and sexual category

<table>
<thead>
<tr>
<th>Baseline (%)</th>
<th>Overall acute (%)</th>
<th>New acute (%)</th>
<th>Highest late (%)</th>
<th>New late (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GU (Any)</td>
<td>193 (65.9)</td>
<td>240 (81.9)</td>
<td>185 (63.1)</td>
<td>213 (75.3)</td>
</tr>
<tr>
<td>Grade 0</td>
<td>100 (34.1)</td>
<td>53 (18.1)</td>
<td>70 (24.7)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>133 (45.4)</td>
<td>198 (67.6)</td>
<td>168 (57.3)</td>
<td>133 (47.0)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>55 (18.8)</td>
<td>39 (13.3)</td>
<td>16 (5.5)</td>
<td>61 (21.6)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>5 (1.7)</td>
<td>7 (3.0)</td>
<td>6 (2.1)</td>
<td>19 (6.7)</td>
</tr>
<tr>
<td>GI (Any)</td>
<td>80 (27.3)</td>
<td>170 (58.0)</td>
<td>149 (50.9)</td>
<td>89 (31.4)</td>
</tr>
<tr>
<td>Grade 0</td>
<td>213 (72.7)</td>
<td>123 (42.0)</td>
<td>191 (67.5)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>72 (24.6)</td>
<td>137 (46.8)</td>
<td>118 (40.3)</td>
<td>67 (23.7)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (2.4)</td>
<td>33 (11.3)</td>
<td>31 (10.6)</td>
<td>23 (8.1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.3)</td>
<td>0</td>
<td>0</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Sexual (Any)</td>
<td>236 (80.5)</td>
<td>250 (81.5)</td>
<td>139 (47.0)</td>
<td>189 (66.1)</td>
</tr>
<tr>
<td>Grade 0</td>
<td>57 (19.5)</td>
<td>142 (47.8)</td>
<td>35 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>108 (36.9)</td>
<td>78 (26.6)</td>
<td>37 (12.7)</td>
<td>151 (53.4)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>114 (38.9)</td>
<td>67 (22.9)</td>
<td>31 (10.6)</td>
<td>88 (31.1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>14 (4.8)</td>
<td>6 (2.0)</td>
<td>2 (0.7)</td>
<td>9 (3.2)</td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; EPE, extraprostatic extension; PSA DT, PSA doubling time; RT, radiotherapy; SVI, seminal vesicle invasion.

39 months. A total of 57 (19%) patients were treated with adjuvant radiotherapy, and 236 (81%) with salvage radiotherapy. All patients completed the prescribed dose. Patient demographics are listed in Table 1.

Toxicity

All patients had baseline and acute toxicity assessments completed. A total of 283 (97%) patients had late toxicities scored, with 10 patients declining further follow-up after treatment. The median number of acute and late toxicity assessments per patient was 8 (range 2–14) and 3 (range 0–17), respectively. A total of 52 (91%) and 262 (89%) patients undergoing ART and SRT had greater than 12 months of follow-up, respectively, while 115 of 160 (74%) patients eligible for 4 years of follow-up had toxicity data available for that period.

Baseline and highest reported grade of acute and late toxicities are shown in Table 2 and summarised below. Prevalence of toxicity at 4 years after PPRT with proportions of patients with change from baseline is detailed for individual toxicities in Table 3.

In summary, acute grade 2–3 GU toxicity was 14.3% compared to 20.5% at baseline, with incontinence being the most common (11.3%) and all other items less than 5%. Acute grade 2–3 gastrointestinal (GI) toxicity was 11.3% compared to 2.7% at baseline, with proctitis (5.8%) and diarrhoea (5.1%) being the most common. Acute sexual toxicity rates decreased across all three items.

Late grade 2–3 GU toxicity occurred at some point during follow-up in 28.3% of patients, with 19.1% being new compared to baseline. Urinary incontinence (24.4%) and cystitis (9.2%) were the most common late grade GU 2 toxicities, with all other items less than 4%. Seven
patients had urethral slings for urinary incontinence, two of which were pre-existing, while five had an artificial urinary sphincter, three of which were pre-existing. Two patients had urethral strictures requiring intervention. For patients with and without baseline grade 2–3 GU toxicity, 4-year prevalence of grade 2–3 GU toxicity was 64.7% compared to 14.3%.

Late grade 2–3 GI toxicity occurred at some point during follow-up in 8.8% of patients, with 8.1% being new compared to baseline. Proctitis was the most common at 4.9%, with one patient requiring argon plasma coagulation.

Late grade 2–3 sexual toxicity occurred at some point during follow-up in 34.3% of patients, with 20.2% being new compared to baseline. Erectile dysfunction was the most common at 28.6%, followed by ejaculatory dysfunction at 15.2%. Two patients had a penile prosthesis at baseline and two had one inserted during follow-up. For patients with and without baseline grade 2–3 sexual toxicity, four-year prevalence of grade 2–3 sexual toxicity was 19.3% compared to 15.5%.

No acute or late grade 4 toxicities were recorded. Four-year prevalence of grade 2–3 GU, GI and sexual toxicities was 25.9% vs. 20.5%, 3.4% vs. 2.3% and 25.9% vs. 14.8% for ART vs. SRT respectively.

**Actuarial toxicity incidence**

The 4-year cumulative incidence of any late grade 2–3/grade 3 GU, GI and sexual toxicity was 32.9%/8.2%, 8.8%/1.2% and 45.5%/4.9%. For ART and SRT, the respective 4-year cumulative incidence rates of any late grade 2–3 GU, GI and sexual toxicity were 29.3% vs. 33.0% ($P = 0.39$), 4.5% vs. 9.5% ($P = 0.67$), and 60.0% and 40.2% ($P = 0.09$), respectively. The 4-year cumulative incidence of any late grade 3 GU, GI and sexual toxicity for ART and SRT was 6.9% vs. 8.7% ($P = 0.48$), 0% vs. 1.6% ($P = 0.45$), and 2.0% and 4.5% ($P = 0.97$) respectively.

**Improvement compared to baseline toxicity**

A proportion of patients had improvement in toxicity from baseline following radiotherapy, as shown in Table 3. Compared with baseline scores, there were higher proportions of patients with improvement compared to deterioration at 4 years after PPRT in the bladder spasm, urinary frequency, urinary urgency, urinary retention and all sexual toxicity items.

**Predictors of toxicity**

On multivariable analysis, salvage intent (HR 1.9, 95% CI 1.0–3.4), baseline grade 2–3 GU toxicity (HR 5.7, 95% CI 3.3–9.8) and acute grade 2–3 GU toxicity (HR 3.4, 95% CI 2.0–5.9) predicted any late grade 2–3 GU toxicity, but not age >65 or ADT. For patients with baseline grade 2–3 GU toxicity, 4-year cumulative incidence of any late grade 2–3 GU toxicity was 79.6% compared to 20.7% for those without.

Age >65, intent and baseline and acute grade 2–3 GI toxicity did not predict late grade 2–3 GI toxicity.

Age >65 (HR 0.6, 95% CI 0.4–0.8), baseline grade 2–3 sexual toxicity (HR 1.6, 95% CI 1.1–2.4) and acute grade 2–3 sexual toxicity (HR 1.8, 95% CI 1.2–2.8) predicted any late grade 2–3 sexual toxicity, but not intent or ADT. For patients with baseline grade 2–3 sexual toxicity, 4-year cumulative incidence of any late toxicity was 50.1% compared to 39.8% for those without.
Discussion

Low rates of post-prostatectomy radiotherapy are reported in Australia, with treatment toxicity believed to be a major factor in poor utilisation. For this reason, the publication of toxicity outcomes for post-prostatectomy image-guided IMRT is thought to be crucial in improving the message our urological colleagues receive. It is particularly important that outcomes are reported following the introduction of new guidelines, such as the eviQ/FROGG consensus guidelines.

Although reports of acute toxicity exist, this series is the first published report of late toxicity outcomes utilising IG-IMRT with implanted fiducial markers and the eviQ/FROGG consensus contouring guidelines. It is also one of the largest published series reporting baseline, acute and late toxicity for men receiving PPRT using a consistent radiotherapy technique with prospectively collected toxicity data. Baseline symptoms are important in analysing late toxicity after pelvic radiotherapy, but these are not commonly reported.

Overall, we found relatively low rates of acute and late toxicity when compared to baseline symptoms, with no grade 4 toxicity. Acute toxicity was reasonable with 14.3% grade 2–3 GU and 11.3% grade 2–3 GI toxicity. For grade 2–3 GU acute toxicity, incontinence had the highest incidence at 11.3%, although lower than baseline rates (18.4%) suggesting ongoing improvement of incontinence even during post-prostatectomy radiotherapy, with 4-year prevalence of grade 2–3 incontinence similar to baseline at 17.4%. This is in keeping with previous reports from the European Organisation for Research and Treatment of Cancer (EORTC) 22911 trial showing no difference in incontinence rates between the ART and observation arms with long-term follow-up.

The prevalence of late grade 2–3 GU symptoms remained stable from baseline to 4 years after PPRT at approximately 21%, predominantly driven by urinary incontinence. The cumulative incidence of late grade 2–3 GU toxicity (32.9% at 4 years) was higher than some series, with a Memorial Sloan Kettering Cancer Centre (MSKCC) series reporting a 16.8% incidence at 5 years and a Princess Margaret Hospital series reporting a 13.2% incidence at 5 years. However, the former did not report whether baseline toxicities were considered, and the latter reported new toxicities. More similar late GU toxicity rates to our series were reported in other series, with a 5-year actuarial incidence of 30–34% reported in a Northern Sydney series published in abstract and a 3-year incidence of 24% in an Italian series. We advise caution in comparing toxicity between PPRT series, as late toxicity rates may take into account pre-existing surgical side-effects, and use of different contouring and treatment techniques with resultant varying PTV sizes can produce results that may not be generalisable to a contemporary cohort using particular guidelines.

Of interest, we found that acute grade 2–3 GU toxicity predicted late grade 2–3 GU toxicity, which may reflect the potential for consequential late effects in the bladder/urethra. Baseline grade 2–3 toxicity predicted incidence of both GU and sexual late grade 2–3 toxicities respectively, and thus baseline symptoms should form part of the discussion with patients about increased risks of late toxicity after PPRT. Indeed, the 4-year cumulative incidence/prevalence of grade 2–3 GU toxicity was 79.6%/64.7% if baseline grade 2–3 GU toxicity was present, compared to only 20.7%/14.3% for the 80% of patients with baseline grade 0–1 GU toxicity. While intent did not predict for grade 2–3 GI or sexual toxicity, we found that salvage intent predicted for late GU toxicity on multivariable analysis, in contrast to previous reports suggesting delayed PPRT may allow improvement in urinary function and quality of life. Especially considering the worse biochemical control seen with increasing PSA prior to PPRT, these results suggest delaying PPRT to decrease late GU toxicity may not be necessary.

The overall prevalence of grade 2–3 GI symptoms at 4 years after PPRT remained stable and low at 2.6%.

The overall prevalence of grade 2–3 sexual toxicity decreased during and after PPRT. Incidence of any late grade 2–3 sexual toxicity was 34.3%, with 20.2% of these new compared to baseline. Nevertheless, prevalence of grade 2–3 sexual toxicity was 16.5% at 4 years after PPRT, decreasing from a baseline prevalence of 43.7%, potentially due to decreased bother as patients become accustomed to sexual dysfunction. ART showed a non-significant trend towards worse sexual toxicity compared to SRT on Kaplan–Meier analysis, in keeping with the improved erectile function recovery with SRT compared to ART seen in other series. This may be due to more time being available for recovery of sexual function.

Adverse events are typically defined as symptoms or signs that are new or worsening compared to baseline, regardless of attribution. Other reports of PPRT toxicity may take into account toxicity at time of consultation after radical prostatectomy and prior to PPRT, leading to lower reported toxicity than the overall rates seen in our series. Despite this, the incidence of new or worsening toxicities in our series is low in comparison to the overall incidence, reflecting the baseline symptoms patients have prior to commencing PPRT. In addition, many patients during late follow-up after PPRT experience an improvement in urinary and sexual function over baseline. Furthermore, quality of life seems stable after PPRT. For these reasons, we question whether cumulative incidence is the best way to report toxicity in this situation.

Although the quality of the evidence comparing radiotherapy and prostatectomy for primary treatment of prostate cancer has been low, recent reports have demonstrated good disease control, quality of life and toxicity with primary radiotherapy compared to...
prostatectomy.\textsuperscript{30–33} Given rates of PPRT over 50% have been reported in patients with high-risk disease\textsuperscript{24} and disease control rates between surgery and radiotherapy in this population are still in debate,\textsuperscript{35} the toxicity seen with PPRT compared to radiotherapy alone should be discussed with patients during consultation for primary therapy. In comparison to toxicity reports after definitive dose escalated IG-IMRT treated at our institution,\textsuperscript{31} higher rates of grade 2–3 GU and GI toxicity were noted in this series (4-year prevalence of 21.7% and 2.6% with PPRT compared to 5-year prevalence of 1.3% and 1.6% after definitive RT, respectively). Much of this toxicity was pre-existing at baseline, reflecting the side-effects patients have already experienced following their radical prostatectomy. It is known that toxicity plays a major role in the decisional regret that patients may experience after radiotherapy,\textsuperscript{36} and the higher rates of toxicity after post-prostatectomy radiotherapy may lead to higher levels of decisional regret. Our own results reflect this, with 16.9% of patients who underwent PPRT having decisional regret about their radical prostatectomy compared to 4.2% regretting their PPRT,\textsuperscript{37} whereas only 3.8% expressed regret after definitive IMRT,\textsuperscript{38} although potentially biased by the ‘failure’ of prostatectomy in requiring PPRT.

Our series has several limitations. Although all patients were contoured by a single radiation oncologist (TPS), the prospective toxicity scoring was performed by a number of staff which may lead to differences in scoring (as is the case in almost every other series). The diarrhoea subscale of the CTCAE scoring system is based on the number of times bowels opened over baseline which may make baseline scoring difficult to interpret, although only 4.8% were scored as grade 1 baseline toxicity. Comparisons with other series are also very difficult due to differences in scoring and reporting. While a recent meta-analysis showed a dose–response relationship for disease control between 60 and 70 Gy,\textsuperscript{39} acute urinary toxicity may also increase with dose escalation,\textsuperscript{40} and surveys of Australian radiation oncologists at recent FROGG consensus workshops (Lehman et al.\textsuperscript{41} and unpublished data, 2017) showed the majority of Australian departments still use 64–66 Gy for PPRT. Our cohort had a planning MRI used for volume delineation and daily image guidance via implanted fiducial markers for treatment. It remains uncertain how our results would compare with departments not utilising these techniques. Baseline toxicity data after ADT commencement and prior to radiotherapy were not widely available, and so the contribution of ADT to changes in GU/GI/sexual function could not be assessed. In addition, we report 4-year toxicity rates, and actuarial incidence may increase over the very long term\textsuperscript{13}; further evaluation is warranted. Finally, with the introduction of PSMA PET imaging,\textsuperscript{42,43} it is possible that target volumes and doses may change in the near future, thus the applicability of our results with these modifications remain uncertain.

Despite these limitations, we report the first large series of late toxicity outcomes utilising the widely adopted eviQ/FROGG consensus contouring and treatment guidelines, and the first reporting late toxicity where image guidance has been achieved using implanted fiducial markers. The results should aid Australian radiation oncologists in their discussions with patients prior to PPRT.

In conclusion, while up to one-third of patients undergoing PPRT using Australian guidelines report moderate or severe late genitourinary and sexual toxicity at some point following treatment, the 4-year prevalence of grade 2–3 GU and GI toxicity overall is virtually unchanged compared to baseline. Patients and referring doctors should be reassured by our findings, and consider the comparative toxicities of definitive and post-surgical treatments at the time of decision making.

Acknowledgements

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References


