# Oncological and urinary outcomes following low-dose-rate brachytherapy with a median follow-up of 11.8 years

*BJU Int* 2022; **130:** Supplement 3: 40–45 doi:10.1111/bju.15845

BJUI
BJU International

Original Article

# Oncological and urinary outcomes following low-dose-rate brachytherapy with a median follow-up of 11.8 years

William John Yaxley[1,2], James Mackean[3,4], Devang J. Desai[5], Gail Tsang[3,4], Judi Dixon[6], Hemamali Samaratunga[7], Brett Delahunt[8], Lars Egevad[9], Robert A. Gardiner[2] and John William Yaxley[2,4,6,10]

*[1]Queen Elizabeth II Jubilee Hospital, [2]School of Medicine, The University of Queensland, [3]Genesis Cancer Care, [4]Wesley Hospital, Brisbane, QLD, Australia, [6]Wesley Urology Clinic, Wesley Hospital, [7]Aquesta Uropathology, [10]Royal Brisbane and Women's Hospital, Brisbane, [5]Toowoomba Hospital, Toowoomba, QLD, Australia, [8]Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand, [9]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden*

## Objectives

To examine the long-term oncological outcomes and urological morbidity of low-dose-rate prostate brachytherapy (LDRBT) monotherapy using live intraoperative dosimetry planning and an automated needle navigation delivery system for the treatment of men with low and intermediate-risk prostate cancer.

## Patients and Methods

A prospective database of 400 consecutive patients who underwent LDRBT between July 2003 and June 2015 was retrospectively reviewed to assess urinary side-effects and biochemical progression, based on the Phoenix definition and also a definition of a prostate-specific antigen (PSA) level of ≥0.2 μg/L.

## Results

Minimum patient follow-up was 5.5 years. The median follow-up of the entire cohort was 11.8 years. The median (range) PSA level was 6.1 (0.9–17) μg/L and the median Gleason score was 3 + 4. The biochemical relapse-free survival (RFS; freedom from biochemical recurrence) based on the Phoenix definition was 85.8% (343/400). The RFS using a 'surgical' definition of a PSA level of <0.2 μg/L was 71% (284/400). Of the 297 men followed for ≥10 years, prostate cancer-specific survival (PCSS) was 98% (291/297). Post-LDRBT urethral stricture developed in 11 men (2.8%, 11/400). For men with ≥10 years of follow-up, 22 men (7.4%, 22/297) required a pad for either stress or urge urinary incontinence (UI). UI was identified in only 2.2% (one of 46) of men who had a bladder neck incision (BNI) before LDRBT.

## Conclusion

LDRBT is associated with excellent PCSS, with a median follow-up of 11.8 years. The risk of post-implantation urethral stricture and UI is low and a pre-implantation BNI for management of bladder outflow obstruction does not increase the risk of UI or urethral stricture.

## Keywords

prostate cancer, low-dose-rate brachytherapy, long-term outcomes, bladder neck incision, urinary incontinence, urethral stricture

## Introduction

Early outcomes of low-dose-rate prostate brachytherapy (LDRBT) based on the Phoenix definition of biochemical failure appear equivalent to the rates of biochemical relapse-free survival (RFS) of a radical prostatectomy for low- and intermediate-risk prostate cancer, with less risk of urinary incontinence (UI) [1–3]. LDRBT is associated with statistically significant improvements in RFS when compared with external beam radiotherapy (EBRT) in intermediate-risk prostate cancer, but not overall survival (OS) [4].

Long-term analyses of patient-reported health-related quality of life (HRQOL) after LDRBT monotherapy are scarce. Early bladder storage symptoms are common but improve with

time [5]; however, UI worsens [6], increasing in one series to 16.3% at 11.7 years [7]. There are very few published papers with a median long-term follow-up of >10 years, particularly with LDRBT as a monotherapy using live intraoperative dosimetry techniques. The LDRBT programme commenced at our institution in July 2003. Unlike most LDRBT programmes, we performed live intraoperative dosimetry calculations followed by the LDRBT implantation using an automatic robotic delivery system during the same intraoperative setting.

The primary objective was to determine oncological outcomes of our first 400 LDRBT cases based on the Phoenix definition of RFS and also on a 'surgical' definition of a PSA level of <0.2 μg/L [8,9] The latter definition is based on the results of gallium-68 prostate-specific membrane antigen positron emission tomography ($^{68}$Ga-PSMA PET)/CT scans on men treated with RT, identifying recurrent disease in a significant proportion below the Phoenix definition [9]. We also aimed to review if a PSA nadir of <0.2 μg/L is associated with a favourable long-term freedom from biochemical cancer recurrence. Secondary objectives included a review of UI and post-LDRBT urological procedures required in men with ≥10 years of follow-up. Finally, we examined if a pre-LDRBT bladder neck incision (BNI) for BOO increased the risk of post-implantation UI.

## Patients and Methods

A prospectively collected single surgeon series of the first 400 consecutive cases of LDRBT using live intraoperative dosimetry techniques on men with low- or intermediate-risk prostate cancer between July 2003 and June 2015. PSA levels were updated annually for men discharged to GP follow-up. UI is defined as the need to wear a pad. Long-term UI outcomes were independently confirmed by the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. Men who did not complete the EPIC questionnaire (54%) were contacted by staff independent of the treating surgeon to confirm continence status based on the EPIC questionnaire and exclude any additional urological procedures performed at other institutions.

A prostate volume of >60 mL was treated with cytoreduction therapy with either androgen-deprivation therapy (ADT; LHRH agonist or oral anti-androgen) or with a 5α-reductase inhibitor (finasteride) for men wishing to decrease the risk of erectile dysfunction. Men with uroflow evidence of BOO were treated with a BNI and resection of any significant median lobe 3–4 months prior to LDRBT. On histology, the location and number of biopsy cores taken in each case and the number of cores positive for carcinoma were recorded, as well as the linear extent of cancer. A Gleason score was recorded for each core. During the study period the Gleason scoring reflected the changes in cancer grading based on the grading criteria of the modified Gleason grading system [10] and the 2014 International Society of Urological Pathology (ISUP) grading system [11]. We continue to report using the Gleason scoring system, as collapsing the Gleason grading system to five groups simplifies the complexity of prostate cancer morphology, with resulting loss of detail of information [12].

The Nucletron SPOT PRO planning software and Seed Selectron delivery system facilitated a single procedure utilising a live implantation technique. The planning system was upgraded in 2011 to Oncentra Prostate. Loose $^{125}$I-BT seeds are contained in cassettes. A biplane transrectal transducer is controlled by the planning system with a motorised needle navigation. An inverse planning algorithm calculates the position of seeds and needles. The robot Seed Selectron system delivers the seed train by using a drive wire along the compose element connected to each needle. No seeds were inserted below the prostate–urethral junction, or outside the prostate capsule. The minimal peripheral dose was 145 Gy. The live intraoperative dosimetry aim was a dose delivered to 90% of the target volume (Target D90) of 160–175 Gy (i.e., 110%–120% of TD = 145 Gy prescription dose) and a percentage of target volume receiving 100% of the prescribed dose (V100) of >95%. For the first 190 cases a post-implantation CT dosimetry study was performed 1 month after LDR implantation, with implantation quality assessed as being of good quality when Target D90 was >145Gy and a V100 of >90% at 1 month, which was consistently achieved. Thereafter, dosimetry was recorded based on the live intraoperative calculations. The Medicare inclusion criteria before 2007 only provided a rebate for men with a Gleason score 3 + 3 and PSA level of <10 μg/L. The inclusion criteria were later relaxed to include Gleason score 7 malignancy.

Three patients moved overseas 1–11 years after their LDRBT and were censored at their last PSA level measurement. Ethics approval for publication was obtained from Uniting Care Human Research Ethics Committee 2019.02.280.

## Results

The patient demographics on presentation are outlined in Table 1. The minimum and median follow-up of the entire cohort is 5.5 years and 11.8 years, respectively. Of the first 190 patients that had 1 month post-implantation dosimetry studies performed, the D90 was >100% in 150/190 (78.9%) and the V100 was >90% in 152/190 (80%). The Phoenix RFS was 85.8% (343/400) and 71% (284/400) had a PSA level of <0.2 μg/L. In all, 31 of the 343 men (9.0%) without PSA failure had a PSA level between 0.5 and 2.0 μg/L.

Phoenix RFS was 82% for men with Gleason 3 + 3 (137/167), 91.5% (162/177) for Gleason 3 + 4, and 78.6% (44/56) for Gleason score 4 + 3. Men with Gleason 4 + 3 were more likely to develop biochemical progression than Gleason 3 + 4 ($P$ = 0.003). The Kaplan–Meier curve for biochemical failure is

**Table 1** Patients' characteristics at baseline.

| Characteristic | Men undergoing LDRBT (*n* = 400) |
|---|---|
| PSA level, μg/L, median (range) | 6.1 (0.9–17) |
| Clinical stage, % (*n*/*N*) | |
| T1b | 0.5 (2/400) |
| T1c | 77.3 (309/400) |
| T2a | 19.3 (77/400) |
| T2b | 3 (12/400) |
| Gleason Score, % (*n*/*N*) | |
| 3 + 3 | 41.75 (167/400) |
| 3 + 4 | 44.25 (177/400) |
| 4 + 3 | 14 (56/400) |
| IPSS at baseline, median (range) | 6 (0–32) |
| Number of prostate biopsies, median (range) | 12 (5–34) |
| Number of positive biopsy cores, median (range) | 3 (1–9) |
| Baseline $Q_{max}$, mL/s, median (range) | 15 (2–53) |
| Prostate volume at time of implantation, mL, median (range) | 35 (16–75) |

shown in Fig. 1, with 297 men followed for ≥10 years after LDRBT.

A PSA nadir of <0.2 μg/L was achieved in 333/400 (83.25%). The PSA level subsequently increased to >0.5 μg/L in 39 men (39/333, 11.7%) at a median (range) of 8 (4–15) years after LDRBT. Progression to Phoenix biochemical failure developed in 16 men (16/333, 4.8%) from this cohort with a median (range) time to Phoenix failure of 12 (9–17) years. The median (range) percentage of positive biopsy cores was 25% (4%–100%). Increasing percentage of positive cores was associated with an increased risk of biochemical failure in Gleason 3 + 3 ($P$ = 0.02), but not Gleason 3 + 4 ($P$ = 0.882) or Gleason 4 + 3 ($P$ = 0.518).

There were 80 men (20%) aged ≤60 years at the time of LDRBT, of which 68/80 had a follow-up of ≥10 years. In the cohort aged ≤60 years, the Phoenix RFS was 89.7%, 96.8% and 80% for Gleason 3 + 3, 3 + 4 and 4 + 3 respectively, and 76.9%, 74.2% and 70% when using a definition of a PSA level of <0.2 μg/L.

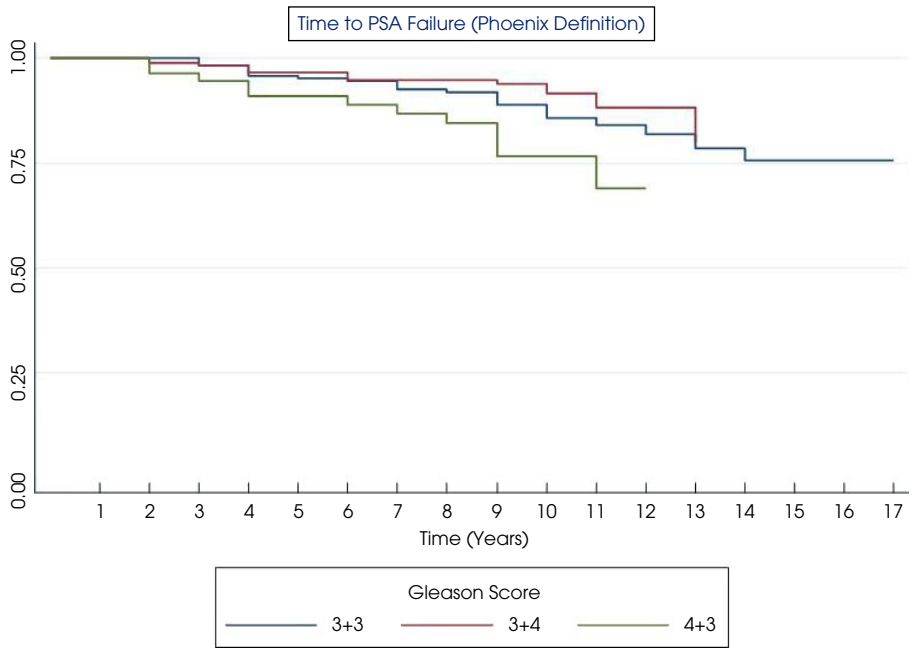
## Mortality Outcomes

Prostate cancer-specific mortality was 1.5% (six of 400) and the mean (range) time to death was 5.5 (4–8) years. Two men developed biopsy confirmed small cell differentiation in association with high-grade recurrent adenocarcinoma and another developed squamous cell malignancy of the prostate. Non-prostate cancer-related mortality occurred in 12.8% (51/400) (Table 1).

## Oncological Outcomes of Men with a Minimal Follow-up of 10 years

A total of 297 men were followed for ≥10 years. The Phoenix RFS was 81.8% (243/297). The OS was 82.8% (246/297) with a prostate cancer-specific survival (PCSS) of 98% (291/297). Using a PSA level of ≥0.2 μg/L as failure, the RFS was 63.1% (94/149) for Gleason 3 + 3, 67.6% (75/111) for Gleason 3 + 4, and 62.2% (23/37) for Gleason 4 + 3.

**Fig. 1** Kaplan–Meier curve for biochemical failure after LDRBT.



Of the 78 men with ≥15 years follow-up after LDRBT, the OS was 67.9%. The Phoenix RFS at ≥15 years was 76.9% (60/78) whereas 62.8% (49/78) had a PSA level of <0.2 μg/L. Of the 297 men with ≥10 years follow-up, 49/297 (16.5%) had between 3 and 6 months of cytoreduction with ADT, 48/297 (16.2%) with finasteride and six (2%) with both. There was no difference in RFS between cytoreduction with either ADT and/or finasteride and men with no pre-LDRBT cytoreduction ($P$ = 0.423).

### Urethral Stricture Risk and Other Post-LDRBT Endourological Procedures

Urethral stricture developed in 11 men (2.8%, 11/400). All men were managed with urethral dilatation, followed by intermittent self-catheterisation. One patient required a long-term suprapubic catheter after transfer to live in an aged care nursing facility.

A cystoscopy was performed on an additional 26 men (6.5%, 26/400) for indications including haematuria (seven of 26) and persisting bladder filling symptoms (four of 26). Three men required surveillance of pre-existing superficial bladder cancer, six men developed superficial urothelial carcinoma of the bladder and two men developed muscle-invasive urothelial carcinoma. A post-LDRBT BNI was required in two patients. Two other patients were treated with a TURP, occurring 4 and 10 years respectively after LDRBT by urologists outside of our centre.

### Long-term UI

For men with ≥10 years follow-up, 22 (7.4%, 22/297) developed either stress or urge UI. Only two men have required surgical intervention, both treated with an artificial urinary sphincter (AUS) at 9 and 10 years after implantation, respectively. The first gentleman had a TURP performed 4 years before LDRBT and the other developed UI after endoscopic management of a urethral stricture.

Five patients had a TURP before LDRBT (1.2–9 years). Three men had no UI, one required an AUS and another was only using a safety pad at 12 years of follow-up.

### Outcomes Following Preoperative BNI

In all, 46 men required a preoperative BNI. The mean (SD) prostate volume was 36.9 (9.1) mL. The mean (SD) maximum urinary flow rate ($Q_{max}$) before BNI was 8.8 (3.9) mL/s and at 1 year after BNI was 12.5 (4.9) mL/s ($P$ < 0.001). The mean (SD) IPSS before BNI was 10.5 (7.8). Three patients (6.5%) developed a urethral stricture. UI developed in one patient (2.2%).

## Discussion

This series represents one of the few publications on oncological and UI outcomes following LDRBT monotherapy with a median follow-up of >10 years. Unlike other long-term LDRBT outcome publications, LDRBT was performed with intraoperative live-planning techniques and free-seed implantation with an automated robotic delivery system. Our results show excellent long-term PCSS and RFS, with a low risk of long-term UI. This is important for men who prioritise continence in their preference for prostate cancer management. We have also identified that a BNI prior to LDRBT does not increase the risk of urethral stricture or UI.

In the Mount Sinai series of 540 men with pre-planned dosimetry and a median follow-up of 12.5 years, the Phoenix RFS was 94% for the low-risk group and 87% for the intermediate-risk group [13]. This compares to our Phoenix RFS of 82% for Gleason 3 + 3 and 91.5% for Gleason 3 + 4. The $^{68}$Ga-PSMA PET/CT results following RT and BT outcomes have shown a high probability of prostate cancer recurrence below the Phoenix definition of PSA failure, including 77% with a PSA level between 0.5–2.0 μg/L [9]. A PSA level of <0.2 μg/L at 4 years after implantation correlates with a 98.7% probability of freedom from biochemical recurrence beyond 10 years. [14]. In the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial, using a RFS of a PSA level of <0.2 μg/L greatly increased the failure of dose-escalated EBRT, but not men treated with an LDRBT boost [15].

One concern confronting physicians is late post-treatment failure, with traditionally only 2% of men receiving salvage treatment [16] due to the significant potential complications of salvage therapies [17,18]. Utilising a PSA of <0.2μg/L as no evidence of biochemical recurrence, in a large retrospective series using pre-plan dosimetry [19], the RFS was 76% and 73% at 10 and 25 years follow-up, respectively. Genebes et al. [20] compared manual BT implantation to intraoperative planning dosimetry and automated implantation and found the automated delivery system was associated with worse dosimetric and RFS outcomes. In contrast, Pons-Llanas et al. [21] found improved biochemical control in 278 men with live real-time intraoperative planning compared to 117 men with preoperative planning. In our LDRBT series, 71% of the entire cohort had a RFS PSA level of <0.2 μg/L and 66.2% for the 148 men with intermediate-risk disease and ≥10 years follow-up. Studies with follow-up of >10 years using intraoperative live-planning techniques are lacking. We therefore believe our results are important, providing evidence that long-term oncological outcomes with live real-time dosimetry and automatic robotic intraprostatic delivery system implantation do not appear inferior to series with pre-planned dosimetry or insertion of BT seeds outside the prostate capsule.

The importance of long-term oncological control increases in men aged ≤60 years at implantation, given a life-expectancy of >20 years [22]. Prada et al. [23] retrospectively reviewed 270 men aged <60 years at LDRBT with a median follow-up of 9.25 years and the Phoenix RFS was 76% in patients with Gleason 3 + 4. Similar results were identified by Winoker et al. [24], although men with intermediate-risk prostate cancer were treated with the addition of 6 months of ADT, or a EBRT boost. In our series using LDRBT monotherapy, men aged ≤60 years with intermediate-risk prostate cancer had a Phoenix RFS of 92.6% (38/41), decreasing to 73.1% (30/41) using a PSA level of <0.2 μg/L.

Post-implantation urinary morbidity is a known complication of BT. In a series of 241 men from Finland, Grade ≥3 urinary toxicity occurred in 10%, requiring surgical intervention mainly for urethral stricture (4.6%) and BOO (4.6%) [25], with similar urinary morbidity was observed in the National Comprehensive Centre Network [26]. In our series endourological procedures were required in 9.3% and urethral strictures occurred in only 2.8%. We do not implant seeds below the apex or outside the prostate. Limiting the dose to the apical and peri-apical urethra can decrease the risk of urethral stricture [27]. Cystoscopy was also required for urological evaluation in 6.5% of men, usually for self-limiting macroscopic haematuria or evaluation of bladder filling symptoms. Six men developed superficial urothelial carcinoma of the bladder and two men developed muscle-invasive bladder cancer.

In the few studies with follow-up >10 years using validated HRQOL questionnaires, LDRBT has less UI compared with a radical prostatectomy, ranging from 4% to 16.3% [7,28,29]. In our series the risk of UI ≥ 10 years after LDRBT was 7.4%. UI that could be associated with dementia or Parkinson's disease, as seen in a few men in our cohort, was still included as a post-LDRBT UI complication.

A TURP before LDRBT can result in a higher risk of post-implantation UI. In the large series by Keyes et al. [26], UI developed in 40% of men with a prior TURP or transurethral incision of the prostate, compared with 1.4% of the entire series. In contrast, in the Uro-Groupe Européen de Curiethérapie (Uro-GEC) phase-II prospective trial of 99 men who had a TURP at least 3 months before prostate BT, the risk of UI was 4% [30]. In our series, men with pre-existing BOO were treated with a BNI ± median lobe resection. Using this technique in our series only one patient (2.2%) developed UI, compared to 7.4% of our entire cohort. Furthermore, only four men (1%) required post-LDRBT endoscopic management of BOO. Two gentlemen were treated at another centre with a TURP, one with subsequent UI. The two patients treated at our centre with a BNI and limited TUR of the prostate floor are continent; however, both developed a urethral stricture. We have shown that urological evaluation and endourological management of BOO before BT has decreased the need for post-implantation TURP/BNI to 1%.

Limitations include the retrospective study design. Also, there were a significant number of low-risk prostate cancer cases treated before 2009, some of which could be considered suitable for an initial period of active surveillance in contemporary urological practice. A single surgeon series can introduce bias with patient selection. However, all but one patient satisfied Government Medicare inclusion guidelines for LDRBT during the study period.

## Conclusion

In summary, we have shown that LDRBT using live intraoperative dosimetry techniques and a robotic automated system for delivery of the BT seeds is associated with excellent PCSS with a median follow-up of 11.8 years. There is pleasing RFS using both the Phoenix definition and the 'surgical' definition of a PSA level of <0.2 μg/L. The risk of post-implantation urethral stricture and UI is low and a pre-implantation BNI for the management of BOO does not increase the risk of UI or urethral stricture.

## Acknowledgements

The authors would like to thank Ricardo Maldonado from PowerStats for performing the statistical analysis. Open access publishing facilitated by The University of Queensland, as part of the Wiley - The University of Queensland agreement via the Council of Australian University Librarians.

## Disclosure of Interests

The authors have no conflicts of interest to declare.

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Correspondence: John William Yaxley, Urological Surgeon, Wesley Urology Clinic, Suite 42, Level 4, Wesley Medical Centre, 40 Chasely St, Auchenflower QLD 4066, Australia.

e-mail: dryaxley@wesleyurologyclinic.com.au

Abbreviations: ADT, androgen-deprivation therapy; AUS, artificial urinary sphincter; BNI, bladder neck incision; BT, brachytherapy; EPIC, Expanded Prostate Cancer Index Composite; $^{68}$Ga-PSMA PET, gallium-68 prostate-specific membrane antigen positron emission tomography; HRQOL, health-related quality of life; LDR, low-dose-rate; OS, overall survival; $Q_{max}$, maximum urinary flow rate; PCSS, prostate cancer-specific survival; RFS, relapse-free survival; (EB)RT, (external beam) radiotherapy; Target D90, dose delivered to 90% of the target volume; UI, urinary incontinence; V100, percentage of target volume receiving 100% of the prescribed dose.