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Modified transurethral resection of the prostate (TURP) for men with moderate lower urinary tract symptoms (LUTS) before brachytherapy is safe and feasible

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Objective

To report the urinary toxicity outcomes for patients at greater risk of voiding symptoms and retention who received a modified limited transurethral resection of the prostate (TURP) before low-dose rate (LDR) brachytherapy.

Patients and Method

Data were analysed from patients receiving the above procedures between 2006 to present, taken from the prospective brachytherapy database of 2000 patients at the St. Luke's Cancer Centre. The limited TURP ($TURP^{BXT}$) was performed at a median (range) of 64 (25–205) days before seed implantation with a median resection weight of 1.15 g. Selection criteria were based on patients with moderate lower urinary tract symptoms, poor flow or post-void residual urine volume (PVR), or a prominent middle lobe or high bladder neck on transrectal ultrasonography. Baseline prostate cancer characteristics, uroflowmetry, International Prostate Symptom Score (IPSS) and quality-of-life QoL scores were collected and compared with follow-up IPSS and QoL scores.

Results

Data for 112 patients was gathered from the database. The $TURP^{BXT}$ resulted in statistically significant improvements before LDR brachytherapy in maximum urinary flow rate (Q_{max}) and PVR, IPSS and QoL scores (the mean Q_{max} before vs after the $TURP^{BXT}$ was 11.3 vs 16.7 mL/s). The IPSS and QoL scores at 6 months after seed implantation were increased compared with baseline values before the $TURP^{BXT}$ (mean IPSS at 6 months 11.7 vs 9.2 before $TURP^{BXT}$), but no difference at 1 year (mean IPSS 9), and improved scores at 2, 3, 4 and 5 years follow-up (mean IPSS of 7.9, 5.6, 5.3 and 7.4, respectively).

Conclusion

The present study suggests patients at increased risk of deteriorating voiding symptoms, including urinary retention, are no longer contraindicated against LDR brachytherapy if they receive a modified TURP before seed implantation. This procedure does not appear to carry the risk of urinary incontinence thought to be associated with a conventional TURP before LDR brachytherapy.

Keywords

brachytherapy, urinary toxicity, TURP, LUTS, prostate

Introduction

Prostate cancer is the most common malignancy in men, affecting 25.6% of those with cancer, and is the second most common cause of cancer death among men in the UK [1]. Prostate brachytherapy has become an established treatment option for organ-confined prostate cancer since Holm et al. [2] described the technique for precise transperineal insertion of radioactive iodine-125 (^{125}I) seeds in 1983. Brachytherapy use has increased significantly in recent years after the introduction of improved imaging and delivery technology, allowing for high oncological efficacy and a low predictable and manageable side-effect profile [3,4], and its use has been endorsed by the National Institute for Health and Clinical Excellence (NICE) guidelines [5].

Brachytherapy is generally well tolerated, although there are recognised side-effects, including LUTS, bowel toxicity and erectile dysfunction, which can have a negative impact on patients' quality of life (QoL) [6–8]. Predictive factors for significant LUTS and urinary retention after brachytherapy have been identified as prostate volume, baseline IPSS, neoadjuvant androgen-deprivation therapy (NADT), and prominent median prostatic lobe hyperplasia [3,9,10]. These

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and other studies have been summarised in patient guidelines on selection for brachytherapy [11].

Historically, guidelines have recommended exclusion of men with large prostates, poor urinary flow rates or significant post-void residual urine volumes (PVRs), high IPSS and those who have had a previous TURP [12]. The initial concern about pre-implant prostatic surgery was highlighted in 1991 by Blasko et al. [13], who reported a high rate of post-implant urinary incontinence (UI; 17%) in patients undergoing TURP for LUTS before brachytherapy. Although more contemporary studies [14] have allayed this concern, with Stone et al. [15] reporting no evidence of UI in such patients, many patients presenting with LUTS and prostate cancer are not being considered for brachytherapy due to the potential increased risk of urinary toxicity [3]. Blasko et al. [13] also proposed that median lobe obstruction does not respond to hormonal modulation, suggesting that a pre-brachytherapy bladder neck resection may be effective in these patients. The aim of the present study was to determine whether a limited modified TURP ($TURP^{BXT}$) before low-dose rate (LDR) brachytherapy seed implantation reduces urinary toxicity.

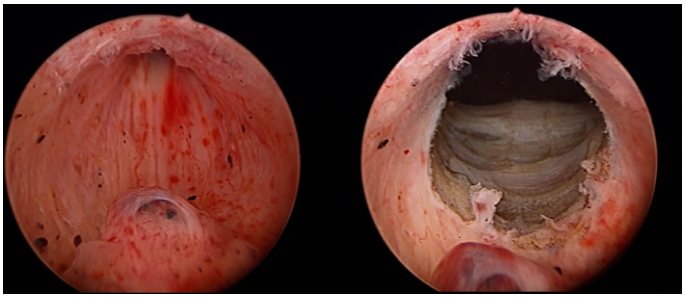
Patients and Methods

The study population was selected from the St Luke's Cancer Centre brachytherapy database of prospectively recorded patient data for >2000 patients. Patients with ≥6 months of follow-up data after LDR brachytherapy seed implantation were eligible for inclusion. Patients who had received NADT and/or external-beam radiotherapy (EBRT) were considered eligible for inclusion in the study population.

Before LDR brachytherapy seed implantation, all patients were assessed for urinary symptoms and symptom bother (QoL), according to IPSS and uroflowmetry (baseline) data. The IPSS has previously been shown to be predictive of post-implant toxicity therefore urodynamics was not performed in patient selection [16]. Patients who had a raised IPSS score (>8), obstructive uroflowmetry (maximum urinary flow rate [Q_{max}] of <15 mL/s and/or PVR of >150 mL), and a prominent bladder neck on TRUS were offered a $TURP^{BXT}$ ~ 10 weeks before their brachytherapy seed implantation. A prominent bladder neck was defined as growth of prostatic middle lobe tissue above a line between the verumontanum and bladder trigone in the sagittal plane on TRUS. TRUS was undertaken at initial assessment for brachytherapy in clinic.

The aim of the $TURP^{BXT}$ was to alleviate BOO, whilst gaining the added advantage of removing prostate tissue that can be technically difficult to implant at the bladder neck. Minimal resection of the lateral lobes was performed to preserve the shape of the prostatic urethra and avoid an irregular cavity that can be difficult to visualise and implant. By resecting only the bladder neck that is distant from the external urethral sphincter the potential for sphincter damage or weakness and subsequent UI is avoided. Patients who underwent a $TURP^{BXT}$ were admitted on a 23-h pathway with an irrigating catheter removed the next morning. Figure 1 shows the endoscopic appearance of the prostate before and after the $TURP^{BXT}$. The median resection weight was 1.15 g.

Fig. 1 Endoscopic views of the prostate before and after the $TURP^{BXT}$.



At our centre a one-stage, real-time TRUS-guided '4D brachytherapy' seed implantation technique was used most recently, using stranded seeds peripherally and loose seeds centrally [17]. This contrasts with uniformly loaded seeds in the first well established descriptions of brachytherapy technique by Grimm et al. [18]. The prescribed minimal peripheral dose was 145 Gy. CT was performed on 1 day after seed implantation to record dosimetry. Those patients who received EBRT initially were given 45 Gy in 25 fractions, followed by a 110 Gy brachytherapy boost 2 weeks later. At the St Luke's Cancer Centre, α-blockers are used routinely for 3 months after seed implantation and then offered therapeutically depending on urinary symptoms thereafter, but typically with an IPSS of >10.

Exclusion criteria for this treatment pathway were men with severe LUTS, or those with intermediate LUTS whose dominant obstruction was lateral lobe hyperplasia. Generally speaking these were men with prostates of >60 mL with or without NADT for 3 months. Whilst patients who had undergone previous TURP would have been considered under the above criteria, there were no such men in the study.

Patients who had had a $TURP^{BXT}$ before ^{125}I brachytherapy at our centre between January 2007 and December 2012 were identified. Demographic and baseline data were collected, which included patient age, clinical stage, Gleason score, prostate volume, pre-brachytherapy urological pharmacotherapy (e.g. α-blocker, 5α-reductase inhibitor) and adjunctive oncological therapy (NADT, boost EBRT). IPSS and uroflowmetry data were collected at presentation, after the $TURP^{BXT}$ and after brachytherapy. Statistical analysis of data was performed using matched *t*-testing and the Wilcoxon rank-sum test as appropriate. Statistical significance was defined by a $P \leq 0.05$.

Table 1 Baseline demographic data.

Variable	Value
Mean (SD):	
Age at brachytherapy, years	67.7 (6.3)
PSA level, ng/	8.1 (3.4)
Prostate voulme, mL	39.4 (11.8)
Brachytherapy parameters	
Mean (SD):	
Modified TURP–brachytherapy interval, days	71 (34.2)
D90, Gy	153 (19)
V100, %	93 (3.3)
V150, %	47 (10)
LUTS parameters	
Mean (SD) Q_{max}, mL/s	11.1 (5.2)
Median (range) PVR, mL	132 (0–554)
Mean (SD) IPSS	9.6 (4.8)
Mean (SD) QoL score	2.2 (1.3)
Gleason score, *n*	
3+2	1
3+3	65
3+4	30
4+3	12
4+4	4
Stage, *n*	
T1c	66
T2a	19
T2b	22
T2c	5
Treament method, *n*	
Brachytherapy	90
Brachytherapy + NADT	17
Brachytherapy + EBRT	5

D90, dose received by 90% of the prostate volume; V100 and V150, percentage volume of the prostate receiving at least 100% or 150% of the prescribed minimal peripheral dose.

Results

Data were collected for 124 out of >2000 patients treated at the Royal Surrey County Hospital who had a TURP^{BXT} before ^{125}I brachytherapy. Patients without pre-brachytherapy IPSS or uroflowmetry data were excluded from analyses, providing 112 patients for analysis.

Table 1 outlines the baseline demographic data including Gleason score and complete treatment regime. Of the 12 patients that received brachytherapy and hormone therapy, nine were given hormones for cytoreduction and three for intermediate-risk prostate cancer (stage ≥T2c, PSA level of >10 ng/mL, or Gleason score ≥7).

TURP^{BXT} Outcomes

Figure 2 shows a statistically significant improvement in all parameters analysed (Q_{max}, PVR, IPSS, QoL score), using paired data from the same patients, as a result of the TURP^{BXT}, before brachytherapy seed implantation.

Complications of the TURP^{BXT} before Brachytherapy

Of the 112 patients in the study, two (2%) patients developed stricture after their TURP^{BXT} requiring urethrotomy and clean intermittent self-catheterisation (CISC), with one further patient requiring CISC for detrusor failure. There were three (3%) episodes of significant haematuria (requiring re-catheterisation and bladder washout); one patient required a repeat TURP^{BXT} because of severe voiding symptoms, who then received brachytherapy. Five patients (4%) developed acute urinary retention (AUR) immediately after TURP^{BXT}, four of whom passed their trial without catheter within a week. One patient as mentioned required ongoing CISC for 6 months, at which point his symptoms settled, he underwent brachytherapy, and did well after seed implantation.

Toxicity after Brachytherapy

Brachytherapy seed implantation was performed at a mean (SD) of 71 (34.7) days after the TURP^{BXT}. Follow-up IPSS data were available at the following intervals: 6 months (101 patients), 1 year (98), 2 years (65), 3 years (38), 4 years (15) and 5 years (eight). Figure 3 shows the mean IPSS and QoL score changes at the above intervals in a paired analysis. Beyond 6 months, there was an improvement in IPSS and QoL score for all intervals. Tables 2 and 3 provide exact data with significance values.

Complications after Brachytherapy

Two (2%) patients needed a repeat TURP^{BXT} (one of whom had presented after brachytherapy with AUR, one who had recurrence of a pre-TURP^{BXT} stricture requiring CISC and then subsequently intravesical botulinum toxin injection). Two additional patients required CISC for stricture.

To date no patients have required surgery for stress UI; we have one recorded case of urge UI successfully treated with intravesical botulinum toxin and no recorded cases of stress UI.

Patients on NADT

There were 22 patients who received NADT before TURP^{BXT}/implantation. Table 3 shows that comparative results were similar to the main group, with lower IPSS and QoL scores at 2–5 years after seed implantation. However, the size of this cohort precluded statistically significant analysis.

Discussion

In the present study there was an improvement in LUTS symptoms, measured by IPSS, in men with mild-to-moderate LUTS who underwent a TURP^{BXT} before brachytherapy at 2–5 years. The TURP^{BXT} was shown to improve patients' LUTS whilst avoiding affecting the external urethral sphincter and so minimising the risk of post-implant UI, with a median resection weight of just 1.15 g. The limited resection also

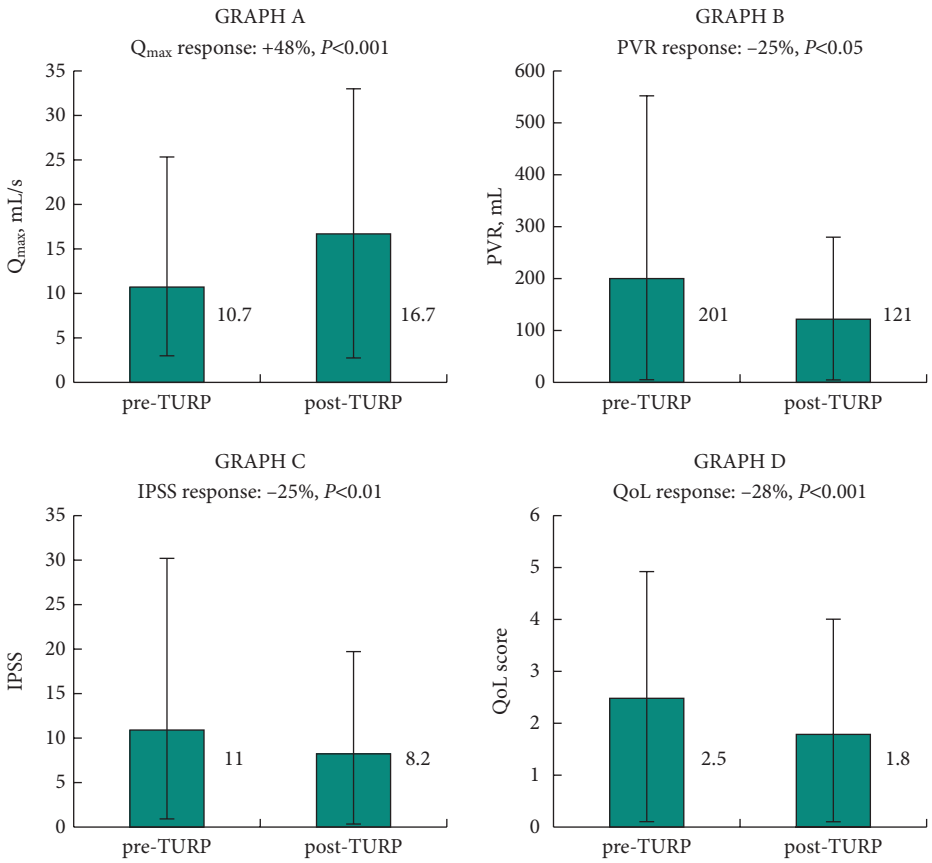


Fig. 2 Paired analysis of mean Q_{max} (A), PVR (B), IPSS (C), QoL score (D) before and after the TURP^{BXT}. Error bars show maximum/minimum.

facilitated seed placement with good dosimetry recorded in the peripheral gland on CT after implantation. We think these results show that a pre-implant TURP^{BXT} gives men with moderate LUTS access to the brachytherapy treatment and avoids the known problems associated with TURP and brachytherapy in combination.

This centre has previously reported on the outcome of the comparative cohort study with matched patients without a TURP^{BXT} [19]. It showed, at 6 months after seed implantation, an IPSS deterioration of just 2.5 points from baseline compared with 6.5 in the matched control group ($P = 0.001$). The results mandated adoption of the technique, as men with moderate LUTS were suffering unacceptable urethral toxicity after seed implantation.

Historically, men with LUTS or previous TURP were not considered for brachytherapy because of concerns about urethral toxicity [20]. Current European guidelines identify men with an IPSS of ≥12 or a prostate volume of ≥50 mL as inappropriate for this method of treatment [21]. Whereas published data exists to justify use of brachytherapy in larger prostates [22,23], the mantra still remains that pre-implant urethral toxicity strongly correlates to post-implant morbidity with respect to LUTS. This technique gives men the option of brachytherapy previously considered inappropriate because of their LUTS.

Recent developments in brachytherapy technique have led to improvements in overall dosimetry, with optimisation of radiation to the apex and a reduction in the urethral dose. At our centre, '4D brachytherapy' has shown a mean reduction in post-treatment IPSS of 2 points compared with the standard Seattle technique [17]. The technique of implanting stranded seeds in the peripheral prostate gland and loose seeds centrally, via the Mick applicator, under direct visualisation in the sagittal TRUS plane as a one stage procedure enables precise seed placement, thereby avoiding excessive doses to structures such as the urethra and penile bulb. Others have adopted 'real-time brachytherapy'; Dallas et al. [22] report a change in IPSS at 1 year of between 0 and 1 compared with the pre-implant baseline value with this technique. These IPSS changes are very similar to those of our TURP^{BXT}, who, with higher pre-treatment symptom scores, would be expected to have higher IPSS scores after implantation [6] than those patients mentioned in the Dallas et al. [22] study. It is unlikely, therefore, that the stable IPSS findings in our present cohort of 'higher risk' patients (of LUTS deterioration) could be explained by improvement in brachytherapy technique.

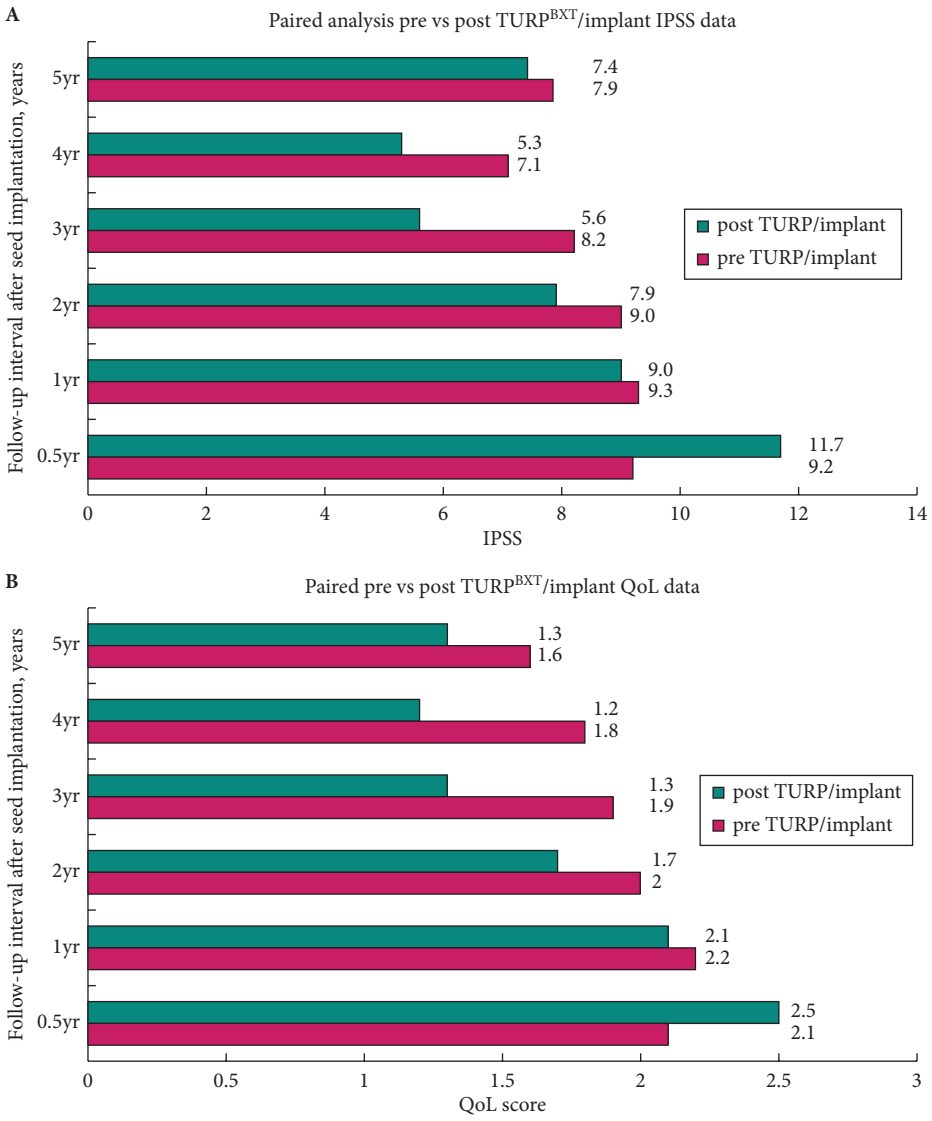


Fig. 3 Paired analysis of IPSS data (A) and QoL score data (B) for patients before and after TURP^{BXT}/seed implantation.

Table 2 Paired analysis of IPSS data (A) and QoL data (B) before and after TURP^{BXT}/implantation.

	6 months	1 years	2 years	3 years	4 years	5 years
Number of patients	101	98	65	38	15	8
IPSS						
IPSS before brachytherapy	9.2	9.3	9	8.2	7.1	7.85
IPSS after brachytherapy	11.7	9	7.9	5.6	5.3	7.42
Difference	2.5	−0.3	−1.1	−2.6	−1.8	−0.43
P	0.001	0.67	0.14	0.004		
QoL						
IPSS before brachytherapy	1.8	1.6	2.1	2.2	2	1.9
IPSS after brachytherapy	1.2	1.3	2.5	2.1	1.7	1.3
Difference	−0.6	−0.3	0.4	−0.1	−0.3	−0.6
P	0.03	0.5	0.06	0.07		

The question therefore falls to whether a TURP should be performed before brachytherapy or after implantation for those with intractable urinary symptoms after implantation. Mock et al. [24] reported a 19% risk of stress UI with standard TURP after seed implantation, rising to 53% in patients with multiple resections. Further, Merrick et al. [25] noted better outcomes in patients undergoing TURP before brachytherapy. Historically, the initial concern about prostatic surgery before brachytherapy was highlighted by Blasko et al. [13] who reported a high rate of UI (17%) after seed implantation in patients who had undergone TURP for LUTS before brachytherapy. It is unclear whether this was true stress UI or whether this was a result of underlying detrusor overactivity. However, other groups have reported a lack of urethral morbidity and UI in such patients. Wallner et al. [14] reported a 6% UI rate at 3 years and no evidence of urethral stricture, and Stone et al. [15] reported no evidence of UI with only 16%

Table 3 Unpaired IPSS and QOL data for patients receiving NADT before brachytherapy.

	Before modified TURP	6 months	1 years	2 years	3 years	4 years	5 years
Number of patients	22	21	19	9	8	3	3
IPSS	7.7	9.4	8	5.3	3.6	1.3	2
QoL score	1.9	2.2	2	1.3	0.8	0.7	0.3

of patients showing cystoscopic signs of mild superficial urethral necrosis at 4 years. The lack of urethral toxicity in these studies may be due to the technique of real-time interactively planned peripheral loading of seeds to avoid high doses to the urethra, while maintaining the prescription central prostate dosimetry. The extent of the pre-implant TURP was also unknown and may be an important factor in post-implant morbidity. Moran et al. [26] reported that brachytherapy after TURP is feasible, with improved urinary bother scores compared with the non-TURP brachytherapy group. Acher et al. [23] also achieved good dosimetric outcomes from brachytherapy implantation after TURP^{BXT} (mean resection weight 4 g). The UI rate in the Moran et al. [26] study was 3% and the best outcomes were seen in patients with pre-implant IPSS scores of ≤8, which is the mean outcome achieved in our present post-TURP^{BXT}/pre-brachytherapy cohort. The UI rate in our present cohort was <1%, consisting of solely urge UI.

The studies mentioned describe the need for a 1-cm margin of residual prostatic parenchyma after TURP for a patient to be eligible for seed implantation [25,26]. Standard TURP is known to produce a variable and unknown prostatic cavity that can hinder subsequent seed implantation. However, in the present study, the TURP^{BXT} spares the lateral lobes whilst removing the cause of the BOO, thereby improving LUTS without creating a large prostatic cavity. Furthermore, the TURP^{BXT} serves to remove tissue at the bladder neck that may be technically difficult to implant, as this tissue can be too thin to allow adequate seed placement, as well as providing diagnostic information about peri-urethral tumour that can guide central prostatic dosimetry prescription.

In the present study, there were no cases of TUR syndrome or blood transfusion, as the operative time was short due to the limited resection performed, of just 1.15 g. In our paired analysis, patients undergoing the TURP^{BXT} had statistically significant improvements in their IPSS, QoL score, Q_{max}, and PVR, before their brachytherapy treatment, providing evidence that the TURP^{BXT} was beneficial to these patients. The best response was seen in prostates glands of <45 mL for whom only a middle lobe resection was necessary. During data collection it was found that the IPSS and QoL score data were not routinely collected in an asymptomatic patient, suggesting that the 4- and 5-year data may be of greater significance than we propose. This may explain the higher than trend 5-year IPSS result. Our present mean 5-year IPSS in the TURP^{BXT} cohort was 7.4 points. This compares to a mean IPSS of 7.9 in a 5–10 years follow-up series of patients that underwent standard brachytherapy at our centre [27]. In all, 2% of our patients required a TURP after brachytherapy seed implantation and there was a single case of urge UI.

The effects of NADT on post-implant LUTS remain unclear. There are data suggesting that NADT detrimentally affects LUTS post-implant [28], with an increased risk of AUR [3], and a correlation with catheter dependence and surgical intervention [29,30]. Other studies suggest that NADT is not a significant predictive factor for catheterisation [31], and patients with large prostates should not be dissuaded from considering NADT followed by brachytherapy [32]. Our present study suggests that patients may tolerate NADT before brachytherapy without deterioration in LUTS, although the small numbers do not demonstrate statistical significance. The decision to offer a TURP^{BXT} at this time is not influenced by the patient's treatment protocol, but by pre-treatment raised IPSS, obstructive uroflowmetry, high PVRs and a high bladder neck on TRUS. We therefore feel that inclusion of these patients is valid.

In conclusion, performing a TURP^{BXT} 10 weeks before LDR brachytherapy seed implantation improved urinary toxicity at 2 years and up to 5 years after seed implantation in selected patients with prostate cancer. This group of patients may otherwise have been advised against brachytherapy as a treatment option due to their poor baseline LUTS.

Conflict of Interest

None declared.

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Abbreviations: AUR, acute urinary retention; CISC, clean intermittent self-catheterisation; EBRT, external-beam radiotherapy; LDR, low-dose rate; NADT, neoadjuvant androgen-deprivation therapy; PVR, post-void residual urine volume; Q_{max}, maximum urinary flow rate; QoL, quality of life; UI, urinary incontinence.

