Original paper

Validation of the bladder neck as an important organ at risk in prostate seed brachytherapy based on D_{2cc}: A single-institution, retrospective review

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Abstract

Purpose: International guidelines recommend urethral dose volume constraints to minimize the risk of urinary toxicity after prostate brachytherapy. An association between dose to the bladder neck (BN) and toxicity has previously been reported, and we sought to evaluate the impact of this organ at risk on urinary toxicity, based on intra-operative contouring.

Material and methods: Rates of acute and late urinary toxicity (AUT and LUT, respectively) were graded according to CTCAE version 5.0 for 209 consecutive patients who underwent low-dose-rate (LDR) brachytherapy monotherapy, with approximately equal numbers treated before and after we began routinely contouring the BN. AUT and LUT were compared in patients treated before and after we began contouring the OAR, and also for those treated after we began contouring who had a D_{2cc} of greater than or less than 50% prescription dose.

Results: AUT and LUT fell after intra-operative BN contouring was instituted. Rates of grade ≥ 2 AUT fell from 15/101 (15%) to 9/104 (8.6%), $p = 0.245$. Grade ≥ 2 LUT decreased from 32/100 (32%) to 18/100 (18%), $p = 0.034$. Grade ≥ 2 AUT was observed in 4/63 (6.3%) and 5/34 (15%) of those with a BN D_{2cc} >/≤ 50%, respectively, of prescription dose. Corresponding rates for LUT were 11/62 (18%) and 5/32 (16%).

Conclusions: There were lower urinary toxicity rates for patients treated after we commenced routine intra-operative contouring of the BN. No clear relationship was observed between dosimetry and toxicity in our population.

J Contemp Brachytherapy 2023; 15, 2: 96–102
DOI: https://doi.org/10.5114/jcb.2023.126315

Key words: LDR brachytherapy, prostate, bladder neck, urinary toxicity.

Purpose

Low-dose-rate (LDR) brachytherapy is a well-established treatment for patients with localized prostate cancer. This may be in the form of monotherapy in case of low or favorable intermediate-risk prostate cancer, or as a component of trimodality therapy for those with higher risk disease. The treatment is associated with good oncological outcomes and a manageable side effect profile [1-5].

The American Brachytherapy Society (ABS) has guidelines regarding dose volume constraints (DVCs) for organs at risk (OARs) at the time of implantation. These include a maximum dose to 5% (D_5) of the urethra < 150% of prescription dose and maximum dose to 30% (D_{30}) of volume < 125% [6]. Groupe Européen de Curiethérapie-European Society for Radiotherapy & Oncology (GEC-ESTRO) recommends a maximum prostatic urethra D_{10} < 150% of prescription dose and D_{30} < 130% [7, 8].

In addition, Hathout *et al*. identified the bladder neck (BN) as an important OAR in their 2014 retrospective review of 927 patients treated with brachytherapy [9]. In that study, D_{2cc} to BN was associated with both acute and late urinary toxicity (AUT and LUT). Higher rates were seen in those with values > 50% of prescription dose, hazard ratio of 1.03 for AUT and 1.01 for LUT. In addition, BN D_{2cc} > 50% was found to be a greater prognostic factor

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Received: 01.11.2022
Accepted: 09.02.2023
Published: 30.03.2023

for acute and late urinary toxicity than conventional DVC to the urethra.

Based on this data, we modified our practice to include routine intra-operative contouring of the BN at the time of iodine-125 (^{125}I) seed implantation for prostate cancer. The purpose of our study was to examine the impact of contouring the BN on rates of urinary toxicity. Moreover, we sought to validate its use as an OAR by assessing toxicity rates based on dose.

Material and methods

Patient and treatment characteristics

We conducted a retrospective review of 209 consecutive patients treated with LDR monotherapy between and March, 2015 and September, 2018. All patients had biopsy-confirmed prostate cancer, and had magnetic resonance imaging (MRI) as part of their staging, unless contraindicated. Full baseline details are displayed in Table 1.

Study design

We recorded clinical, dosimetric, and toxicity data for 209 consecutive patients treated with definitive monotherapy for prostate cancer. This included at least 100 patients who were treated both before and after we began routinely contouring the BN intra-operatively.

Our primary interest was whether rates of grade ≥ 2 AUT and LUT changed after we began contouring the BN, and aiming to keep the dose to this novel OAR as low as achievable.

Secondly, we examined the constraint which Hathout *et al*. [9] had identified as a predictor for AUT and LUT by comparing rates of grade 2+ AUT and LUT in patients whose BN D_{2cc} was > or ≤ 50% prescription dose. The study was approved by the hospital's research ethics committee.

Brachytherapy technique

Three different brachytherapists performed the procedure during the study period, but the majority were undertaken by one clinician. The patients were under anesthesia, either general or, less frequently, spinal. They were catheterized for the duration of the procedure and received anti-microbial cover at the time of anesthetic induction only. Insertion of transperineal interstitial needles to the prostate gland was aided by a perineal template, and performed under image-guidance via axial and sagittal TRUS images.

The prostate, rectum, and urethra were contoured on axial ultrasound slices and transferred to the brachytherapy planning system. The urethra was contoured with assistance of trans-urethral aerated gel. The method for contouring the BN was described in detail in Hathout's

Table 1. Baseline characteristics

Characteristic	Before (group 1)	After (group 2)
Total	101	108
Age, median (IQR)	65 (60-68)	66 (60-69)
Stage (clinical/radiological), *n* (%)		
T1c	15 (15.1)	23 (22.3)
T2	82 (82.8)	79 (77.0)
T3a	2 (2.02)	1 (0.97)
Not available	2	5
Gleason score, *n* (%)		
6	44 (43.6)	43 (40.6)
7	56 (55.4)	62 (58.5)
8	1 (0.99)	1 (0.94)
Not available	0	2
Pre-treatment PSA, median (IQR)	7.07 (5.74-8.98)	7.05 (5.80-9.39)
Gland volume (cc), median (IQR)	30 (25-36) (missing = 9)	35 (29-41) (missing = 3)
Neoadjuvant ADT, *n* (%)	8 (7.9) (missing = 1)	7 (6.5) (missing =3)
Baseline IPSS, median (IQR)	6 (2-10)	4 (2-8)
Baseline use of pharmacotherapy for LUTS, *n* (%)	2 (1.98)	3 (2.78)
Comorbidities, *n* (%)		
Diabetes	8 (7.9)	7 (6.5)
Current smoker	9 (8.9)	8 (7.4)
Ex-smoker	23 (22.7)	15 (13.9)
Never smoked	57 (56.4)	75 (69.4)
Unknown smoking status	4 (4.0)	10 (9.3)

paper [9] and, in short, it is a 5 mm isometric expansion around the Foley catheter, as defined by the aerated gel, distal to the catheter balloon, proximal to the prostatic urethra, and expanded to a minimum volume of 2 cc.

Iodine-125 seeds were used for all patients, and the prescription dose was 160 Gy to the prostate without a margin. Needles were placed with reference to template coordinates. Loose seeds were placed peripherally via a Mick applicator, and real-time dosimetry via a nomogram-based technique was evaluated using VariSeed planning system to guide placement of the central needles and seeds. Constraints for treatment included a volume percentage of the prostate receiving 100% of prescription dose (V_{100}) > 95%, prostate D_{90} > 100%, and rectum V_{100} < 1 cc. We considered a D_{2cc} ≤ 50% to be an optimal constraint for the BN based on Hathout's study.

After completion of the seed implant, the catheter was removed and the patient was transferred to the recovery room. Patients were given an α-blocker in recovery and discharged later the same day with a three-month prescription for the same medication.

Outcome measurement

Patients completed an international prostate symptom score (IPSS) questionnaire at their initial consultation before brachytherapy. Follow-up appointments were scheduled at 1, 3, 6, and 12 months after the procedure, and either 6 monthly or annually thereafter. At each outpatient visit, clinical information was recorded regarding patients' subjective recording of symptoms reflecting toxicity.

For the purpose of this study, medical records were reviewed and urinary toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0. In a minority of cases, clinicians had assigned CTCAE scores at the time of review. Otherwise, these were graded by the author reviewing the medical records. The CTCAE contains multiple domains under the category of 'Renal and Urinary Disorders', and this was applied as a guide. The worst score in any of these domains was used to assign a grade of urinary toxicity for each clinic visit. For example, a need for medical management for urinary frequency was categorized as grade 2. Need for tamsulosin was also considered grade 2. According to CTCAE, minor toxicities are generally grade 1, whereas moderate toxicities are generally grade 2. Although retrospective, the medical records typically provided sufficient information to make this evaluation. IPSS questionnaires were not routinely issued to patients at follow-up visits. This practice has changed since these patients were treated, but post-therapy IPSS scores are only available for a small minority of patients.

AUT was defined as urinary toxicity reported within 3 months of the procedure, and LUT was urinary toxicity reported beyond 3 months.

Statistical analysis

We applied medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. A comparison of AUT and LUT before and after we began contouring the BN was performed using a χ^2 test. Rates of AUT and LUT, and pre- and post-therapy IPSS scores, for those with BN D_{2cc} of > and ≤ 50% were also analyzed with χ^2, or Fisher's exact test when data were sparse. A significance level of 0.05 was applied in all cases.

A relationship with other potential predictive factors for urinary toxicity was assessed by independent-samples Mann-Whitney *U* test.

Results

A minority of patients were seen only once or not at all after the procedure, as they opted to continue their follow-up with a referring hospital. Results were available: AUT for 205 patients (98%) and LUT for 200 (96%). Median follow-up was 42.9 months (IQR, 28-53 months) prior to introduction of contouring of the BN, and 31.2 months (IQR, 9-37 months) afterwards.

Twenty-four (12%) patients experienced grade 2 AUT, and no patient had grade 3 AUT or above. There were 47 (23%) and 3 (2%) patients with grade 2 and grade 3 LUT, respectively. No episodes of grade 4 or 5 toxicity were observed.

Values before and after institutional contouring of the BN

Table 2 demonstrates outcomes before (group 1) and after (group 2) institutional contouring of the BN commenced. Grade 2-3 AUT reduced from 15/101 (15%) to 9/104 (8.7%), $p = 0.245$. LUT reduced from 32/100 (32%) to 18/100 (18%), $\chi^2 = 4.5$, $p = 0.034$. All except 3 of these toxicities were grade 2 in severity, and all grade 3 toxicities occurred in patients who were treated without BN contouring.

Five patients experienced urinary retention, of whom three were treated without BN contouring. A Fisher's exact test indicated no statistically significant association between BN contouring and acute or late urinary retention, $p = 0.674$ ($n = 209$); although it should be noted that the number with urinary retention was very small.

5/209 patients ($n = 5$; missing = 9) were taking alpha blockers or other pharmacotherapy for lower urinary tract symptoms (LUTS) at baseline. 42/101 (42%) patients

Table 2. Toxicity rates without and with a contoured bladder neck

Group	*n*	AUT data available	AUT grade 2-3	LUT data available	LUT grade 2-3
Group 1 (before contouring)	101	101	15 (15%)	100	32 (32%)
Group 2 (after contouring)	108	104	9 (9%)	100	18 (18%)
Difference			$p = 0.245$		$p = 0.034$

treated without BN contouring and 33/108 (31%) of those treated with a contoured BN had a new requirement for such medications extending 3 months or more after the procedure. The difference was not statistically significant ($p = 0.243$).

Toxicity rates for those with D_{2cc} > and ≤ 50%

Baseline characteristics for the patients treated after we began contouring the BN are displayed in Table 3.

Of these 108 patients, 67 (66%) had values > 50% of prescription dose, and 34 (34%) had values ≤ 50%. Data were missing for 7 patients.

No episodes of grade 3+ toxicity were seen in this population. Grade 2 AUT rates were 4/63 (6%) for those with D_{2cc} > 50% and 5/34 (15%) with D_{2cc} ≤ 50% of prescription dose, $p = 0.270$. Grade 2 LUT was reported in 11/62 (18%) patients with D_{2cc} > 50% and 5/32 (15.6%) with D_{2cc} ≤ 50% of prescription dose, $p = 1.0$ (Table 4).

Association of other variables with toxicity

A Mann-Whitney *U* test revealed a statistically significant association between IPSS pre-implant score and grade 2-3 LUT. Those with grade 2-3 LUT had a higher score (median, 7) than those who did not develop grade 2-3 LUT (median, 4) ($n = 188$, $p = 0.001$). Of the 5 patients with grade 3 LUT, scores ranged from 3 to 22. No significant association was observed between urethra D_{30}, prostate D_{90}, or gland volume, and AUT or LUT.

Discussion

We observed lower rates of urinary toxicity after the introduction of routine intra-operative contouring of the BN. However, there was no clear predictive relationship between dose and toxicity. Our absolute rates were also lower than those previously reported [9].

LUT rates were significantly lower in those patients who were treated with their BN contoured as an OAR. Rates of AUT and prolonged requirement for pharmacotherapy for urinary symptoms were also lower, although not statistically significantly.

However, the comparison of results for those with a BN D_{2cc} of > or ≤ 50% of prescription dose did not suggest that the improved clinical outcomes were related to BN dose. This finding is consistent with a retrospective review of patients treated with high-dose-rate (HDR) brachytherapy, which also did not identify a correlation between BN D_{2cc} and urinary toxicity [10]. Whether the HDR experience has any relevance to the LDR population is unclear. Dose-sensitive OARs may differ between the techniques.

On the other hand, dose to the internal urinary sphincter, as defined by MRI, was correlated with acute urinary bother in a US cohort of 42 patients treated with LDR monotherapy [11]. Our rates of urinary catheterization were in line with the published literature in this area [12, 13].

Possible explanations for our findings and difference from Hathout et al. [9]

The groups treated before and after we began contouring the bladder neck appeared to have similar clinical characteristics. The higher toxicity rates observed in patients treated without the BN contoured may reflect increasing operator experience, hot spots in the region of the urethra, or may simply be the result of chance due to the small numbers involved. In addition, our prescription dose of 160 Gy was higher than Hathout's, which may have influenced why BN D_{2cc} was not predictive in our cohort.

Table 3. Baseline characteristics for BN D_{2cc} >/≤ 50% prescription dose

Characteristic	D_{2cc} ≤ 50%	D_{2cc} > 50%
Total	34	67
Age, median (IQR)	66.5 (62-69)	65 (60-69)
Gland volume (cc), median (IQR)	35 (31-40)	35 (29-42)
Neoadjuvant ADT, *n* (%)	1 (2.9)	5 (7.5)
Baseline IPSS, median (IQR)	3 (2-6.5) (missing, *n* = 5)	4.5 (2-9) (missing, *n* = 9)
Baseline use of pharmacotherapy for LUTS, *n* (%)	2 (5.9)	3 (4.5)
Comorbidities, *n* (%)		
Diabetes	2 (5.9)	5 (7.4)
Current smoker	2 (5.9)	5 (7.4)
Ex-smoker	5 (14.7)	10 (14.9)
Never smoked	23 (67.6)	46 (68.6)
Unknown	4 (11.8)	6 (9.0)

Table 4. Toxicity rates for BN D_{2cc} >/≤ 50% of prescription dose

Bladder neck D_{2cc}	*n*	AUT results available	Grade 2 AUT	LUT results available	Grade 2 LUT
> 50% prescription dose	67	63	4 (6%)	62	11 (18%)
≤ 50% prescription dose	34	34	5 (15%)	32	5 (16%)
Difference			$p = 0.270$		$p = 1.000$

Table 5. Literature on bladder neck as a predictor for urinary toxicity after prostate brachytherapy

Study	Design	Patients	Brachytherapy	Contouring method	Findings
This study	Retrospective cohort	209	LDR monotherapy	Ultrasound-guided (intra-operative)	Grade 2-3 AUT 15% without contoured bladder neck vs. 9% with; Grade 2-3 LUT 32% without contoured BN vs. 18% with; AUT 6% with D_{2cc} > 50% and 15% with $D_{2cc} \leq 50\%$ prescription dose; LUT 18% > 50% and 16% ≤ 50% prescription dose
Hathout *et al*., 2014 [9]	Retrospective cohort	927	LDR alone or LDR and supplemental EBRT	Day 0 CT	HR for grade 2-3 AUT 1.03 for D_{2cc} > 50% prescription dose HR = 1.01 for grade 2-3 LUT
Smith *et al*., 2011 [17]	Prospective cohort	159	LDR with caesium-131	Unclear	Dmax predicts for urinary toxicity; higher rates of urinary retention with D_{max} > 145 Gy
Sanmamed *et al*., 2019 [16]	Phase II trial	61	EBRT and HDR boost	MRI-guided	No association between BN D_{max} and grade 2+ AUT (OR = 1.03, 95% CI: 0.98-1.09%, p = 0.218); 3/4 episodes of urinary retention occurred in patients with BN D_{max} in highest quartile
Ben Aicha *et al*., 2020 [10]	Prospective cohort	309	EBRT and HDR boost	CT- or ultra-sound-guided intra-operative	No correlation between BN D_{2cc} and early IPSS (p = 0.798), late IPSS (p = 0.859), or urinary retention (p = 0.272)

The vast majority of implants were performed by a single operator, and the outcomes may improve over time as a result of increased experience. This may not necessarily be reflected in DVCs seen at the time of implantation, but similar findings have previously been reported regarding declining rates of urinary retention as operators gain experience [14]. It may be that the slight change in technique introduced by BN contouring may have had some influence on outcomes aside from dosimetric changes.

An advantage of the generating the urethral expansion intra-operatively is that it helps to guide seed placement. It allows for visualization of the urethra when implanting seeds in the sagittal view, and thus acts as a prompt as to the proximity of the urethra. As a result, performing the procedure with the BN contoured may reduce the likelihood of placing seeds in close proximity to the urethra. This may reduce the risk of significant hot spots in its vicinity, which may not be reflected by the BN D_{2cc}. Significantly elevated doses in close proximity to the urethra have previously been shown to correlate with rates of urinary toxicity [15], and it is possible that the BN has similar properties.

We recognize that there may be a difference in ultrasound-based contouring with the patient in the dorsal lithotomy position, as opposed to at CT where the patient is in the supine position. There is incomplete drainage of urine against gravity at this time of the procedure, whereas the catheter can drain more freely in the supine position at the time of CT. It is possible that this would result in a slightly different contour. However, it seems unlikely that any such difference would have been so great as to fully explain the differences between our results and those of Hathout's [9].

Strengths

To our knowledge, this is the first report of outcomes based on intra-operative ultrasound-based contouring of the BN and its usage as an OAR. The patient cohort was treated sequentially, and all patients treated with monotherapy over this timeframe were included. This is an actual population of patients undergoing brachytherapy in a tertiary referral center.

Limitations

It is difficult to retrospectively grade toxicity and this is perhaps the greatest weakness of the present study. We were reliant on individual recording in clinical practice in the absence of express guidance on how toxicity should be recorded. For the purpose of this study, two authors were involved in the retrospective grading of toxicity rates but, given the limitations, our absolute toxicity rates could not be considered externally valid. Toxicities for all patients within the population were assessed in the same way, so comparisons within our population subgroups can be considered valid. Consistent prospective recording according to a set standard, including CTCAE, or a patient-reported outcome, such as the IPSS, would have been a more reliable metric. However, these were not available for this population.

In addition, the absolute number of patients involved was reasonably small, which reduced our power to detect a difference between the groups with higher or lower

BN D_{2cc}. Many referrals came from outside institutions, which impacted the availability of results for LUT. Follow-up time was also longer in the group treated without their BN contoured. This had little impact on the results for AUT, but may have contributed to underpowering results for LUT. However, the majority of patients who developed LUT in our population had done so before 12 months, and the group treated after we began contouring the BN had a median follow-up of 15 months. Therefore, it seems unlikely that a shorter duration of follow-up could fully explain the significantly lower rates of LUT observed in that group.

Implications for practice

These data were collected retrospectively and lend limited support to the prior findings by Hathout *et al*. [9], but the overall literature in this area is conflicting (Table 5). A prospective phase 2 trial (n = 61) examining the impact of BN dose in the context of MRI-guided high-dose-rate prostate brachytherapy also demonstrated no obvious link between a high BN dose and grade 2 AUT or above [16]. BN doses within the highest quartile of the population were observed in 3 of 4 patients with urinary retention in that trial. The small sample size is a limitation of that study, and it is hard to know how applicable those results are to ours given the different dose-rate. On the other hand, a cohort study evaluating predictors of urinary toxicity in 159 patients treated with caesium-131 prostate brachytherapy identified the BN maximum dose as the only consistent dosimetric predictor of toxicity [17].

GEC-ESTRO [7, 8] and the American Brachytherapy Society [6] have recommended constraints for the urethra when performing this procedure. Associations between other factors, including baseline IPSS, larger prostate size, greater number of implanted needles, use of neoadjuvant androgen-deprivation therapy, and a higher prostate D_{90} with higher rates of urinary toxicity have been reported [10, 18-20]. Dose to the lower bladder and trigone have also been linked to rates of urinary toxicity using external beam radiotherapy [21].

Looking at other potentially predictive factors in our population, we noted greater rates of toxicity in those with higher baseline IPSS values, but no association with other variables. We did not identify any specific peri-implant constraints which were associated with lower rates of urinary toxicity.

There is no obvious detriment to contouring the BN and striving to limit the dose it receives, especially in those with high baseline IPSS. MRI guidance may help with more accurate delineation [16]. Additional prospective studies examining toxicity rates would further help to evaluate the BN as an OAR during prostate seed implantation.

Conclusions

Increased scrutiny of the dose received by the BN at the time of permanent LDR brachytherapy seed implantation was associated with lower rates of urinary toxicity in this single-institution retrospective analysis. No association was observed between BN D_{2cc} and rates of AUT or LUT. Our findings suggest that contouring the BN at the time of implantation is a worthwhile practice. However, they are not sufficient to validate the use of ≤ 50% prescription dose as a DVC, or indeed to suggest any particular DVC.

Acknowledgements

The authors would like to acknowledge the Department of Medical Physics at Cork University Hospital for their assistance throughout this study. In addition, St Luke's Institute for Cancer Research (SLICR) provided support with statistical analysis, and we would also like to acknowledge them.

Disclosure

The authors report no conflict of interest.

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