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URETHRAL SURVEILLANCE AFTER RADICAL CYSTECTOMY: A 10-YEAR REGIONAL EXPERIENCE

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Abstract

Introduction

Radical cystectomy (RC) is commonly performed with curative intent for primary or recurrent high-risk non-muscle-invasive and muscle-invasive bladder cancers. Urethral recurrence (UR) within the residual urethra, often proximally where the epithelial lining comprises urothelial cells, is a rare but well-described occurrence associated with adverse clinical outcomes. Current national guidelines therefore suggest that male patients with a defunctioned urethra should undergo annual endoscopic or urethral washing surveillance for 5 years following RC, to identify UR early, where local disease management (e.g., urethrectomy) may still be possible. Anecdotally, however, urethroscopy and urethral washing cytology appear to be infrequently performed. Our regional trainee-led research collaborative evaluated the frequency and timing of urethral surveillance in the West Midlands in comparison to National Institute for Health and Care Excellence (NICE) guidelines.

Patients and methods

Our 10-year cross-sectional retrospective regional analysis included 495 patients from 2008–2018. Clinical and demographic data were collected alongside cross-sectional staging and imaging, and timings and frequency of urethral endoscopic surveillance or urethral washing cytology.

Results

Overall, 159 (35.2%) patients received one (or more) surveillance urethroscopy. A minority of surveillance urethroscopies were annual, with hugely variable frequency or intervals ranging from every 4–50 months. Only 81 (19.6%) patients had urethral surveillance in keeping with the frequency suggested by NICE guidelines. At 10 years, disease-specific mortality was 42.0%, and overall or all-cause mortality was 44.7%. The overall UR rate (as detected by staging CT and/or urethroscopy) was 1.0% (n = 4); all four cases of UR were found in patients with positive urethral margins after RC who did not undergo immediate urethrectomy.

Conclusions

Our regional urethral surveillance practice following RC is heterogeneous and suboptimal in comparison to NICE guidelines. Our UR rate was so low that we are unable to assert whether early detection has any clinical benefit, and therefore we cannot advocate routine urethral surveillance, but suggest that patients

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with positive urethral margins should be offered immediate urethrectomy post RC. In addition, we encourage collaborative urological research and data collection to generate higher volume series, more representative and generalisable data, and more meaningful conclusions.

Keywords: *bladder cancer; urethral surveillance; NICE guidelines*

INTRODUCTION

Approximately 2100 radical cystectomies (RCs) are performed each year in England with curative intent, for primary or recurrent non-muscle-invasive (NMIBC), or muscle-invasive bladder cancers (MIBC).[1] Following RC, local tumour recurrence within the residual urethra, often proximally where the epithelial lining still comprises urothelial cells, is a rare but well-described occurrence.[2] Urethral recurrences (URs) are widely considered as heralds of poor prognosis, and have been reported as associated with significantly increased risks of local invasion, metastatic disease, and increased disease-specific mortality (55–75% within 28 months of detection).[3,4]

Risk factors for UR include large volume and multifocal tumours, the presence of bladder carcinoma in-situ (CIS), and bladder neck and/or prostatic urethral involvement.[2,4] UR can be mitigated by urethrectomy; however, this is infrequently performed concurrently with RC due to associated additional anaesthetic time, procedural morbidity, and implication for neobladder construction.[5] Following RC, however, positive urethral margins and extensive CIS, for example, may prompt early urethrectomy to reduce the risk of local UR.[3–5]

Given the potential mortality associated with UR and the low frequency of primary urethrectomy performed concurrently with RC, the National Institute for Health and Care Excellence (NICE) guidelines suggest annual urethral washing cytology and/or direct visualisation of remaining urethral mucosa with urethroscopy for 5 years, as part of post-RC surveillance.[6] Such surveillance is considered particularly important as local (urethral) recurrence may precede nodal or metastatic spread, therefore if identified early, there is a potential opportunity for local management or disease control (e.g., urethrectomy or radiotherapy) before progression occurs.[4,7]

The reported rate of UR in series is historically highly variable, from 10 to almost 40%,[8] reflecting wide variation in methods and timings of post-RC surveillance practices. However, more contemporary reports have suggested that the rate of UR is lower, from approximately 1 to 14%, perhaps reflecting the wider use of neoadjuvant chemotherapy (NACT) prior to RC and high all-cause mortality in this cohort with recent trends towards offering radical treatment for more elderly and comorbid patients, with the consequent shorter period of time within which UR can be detected.[5,8,9] Furthermore, and as suggested in the NICE guidelines, variation in reported UR rates and the lack of robust data from high-volume series with homogeneous patient populations and surveillance protocols are almost certainly contributing to the currently observed national disparity in follow-up practices, which is impacting upon how readily and when we identify URs.[6]

We analysed our regional 10-year post-RC surveillance data with the aim of determining our regional UR rate and to evaluate our regional surveillance practices. Specifically, we aimed to identify the number and frequency of urethroscopies, and other means of urethral surveillance performed following RC. We hypothesised that adherence to national guidance in surveillance was suboptimal, but anecdotally the risk of UR leading to mortality was so low that it perhaps did not justify the follow up currently recommended.

PATIENTS AND METHODS

A total of 495 patients were included from four centres across the West Midlands (University

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Hospitals of Coventry and Warwick, University Hospitals Birmingham, Wolverhampton New Cross Hospital and University Hospitals of North Midlands). All centres obtained local departmental and Clinical Audit approval.

Radical cystectomies performed between 2008 and 2018 were included. Clinical and demographic data were recorded. This included age at RC, gender, pre-operative pathological and radiological staging, post-operative staging and histology, and methods and frequency of surveillance. Regional performance was measured against NICE recommendations in Guideline NG2: Bladder cancer: diagnosis and management (Section 1.6.2), of "*consider.... for men with a defunctioned urethra, urethral washing for cytology and/or urethroscopy annually for 5 years to detect urethral recurrence*."[6]

Microsoft Excel (Microsoft Corporation, USA, v16.0, 2016) and online Social Science Statistics software were used for statistical analyses.[10] Multivariate regression was used to identify potential high-risk groups for UR ($P < 0.05$ considered significant); otherwise, simple descriptive methods were used.

RESULTS

Demographics

As shown in Table 1, 495 male patients were included for analyses. Median age was 71, range 30–90. Median follow up was 32 months, range 1–134. About 232 (47.1%) radical cystectomies were performed for MIBCs (five were salvage following chemoradiotherapy), 57 (11.5%) for primary bladder CIS, and 205 (41.4%) for primary or recurrent (high-risk) NMIBC. One case of presumed MIBC was identified histologically as metastatic colorectal cancer following RC.

Post-operative pathological staging for bladder (data available for all cases) and prostatic urethra (data available for 412 cases) is shown in Figure 1. Thirty two of 412 (8.2%) cases had positive urethral margins (including the presence of CIS). Of these 32 cases, 13 underwent immediate urethrectomy; all 13 were alive at the conclusion of data collection.

Urethroscopy surveillance rate

Overall, of the patients still alive and residing within the West Midlands more than 6 months post RC (n = 412), 159 (35.2%) patients received one (or more) surveillance urethroscopy, 111 (25.7%) received at least two, 79 (19.2%) received three, and 47 (10.7%) received four (Figure 2). The minority of surveillance urethroscopies were annual, with hugely variable intervals ranging from every 4–50 months.

Urethral washings

Eight patients had urethral washings taken during urethroscopy (all at first urethroscopy). One case returned atypical cells (Paris classification), which prompted local management with mitomycin gel. No patients had urethral washing cytology performed instead of urethroscopy.

Overall urethral surveillance

Excluding patients who had upfront urethrectomy, patients whose data were missing (e.g., patient moving out of area) and accounting for mortality over the follow-up period, only 81 (19.6%) of them

TABLE 1 Patient Demographics

Age	**Range 30–90 years**	**Median 71 years**		
Patient number by site*	UHB: 173	UHCW: 122	UHNM: 101	WNC: 99
Reason for cystectomy	232 MIBC (47.1%)	205 NMIBC (41.4%	57 CIS (11.5%)	5 Salvage (MIBC)
Follow up	Range 1–134 months	Median 32 months		

CIS = carcinoma in-situ; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle-invasive.
**UHB = University Hospitals Birmingham; UHCW = University Hospitals of Coventry and Warwick; UHNM = University Hospitals of North Midlands; WNC = Wolverhampton New Cross.*

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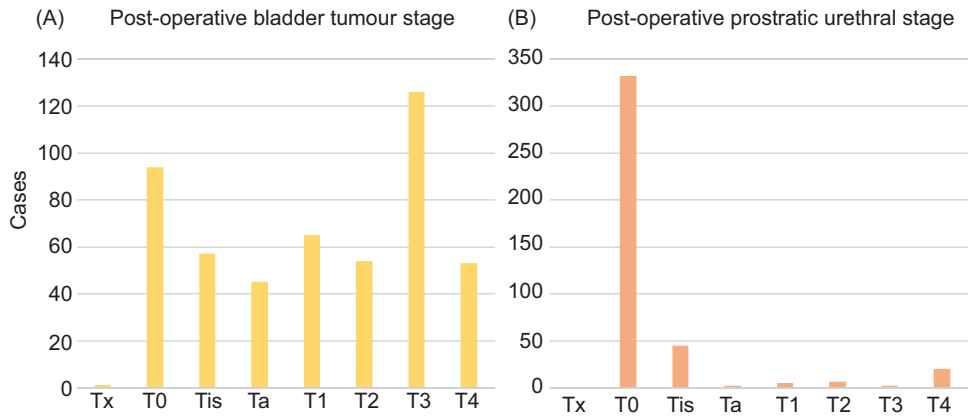

FIGURE 1 Bladder and urethral staging. (A) Bar graph demonstrating the radiological T stage of the bladder tumour(s) following radical cystectomy (RC). (B) Bar graph demonstrating the radiological T stage of the prostatic urethra following RC.
Tx = unable to be assessed; T0 = no residual tumour; Tis = carcinoma in-situ; Ta/T1 = tumour confined to urothelium; T2+ = muscle invasive.

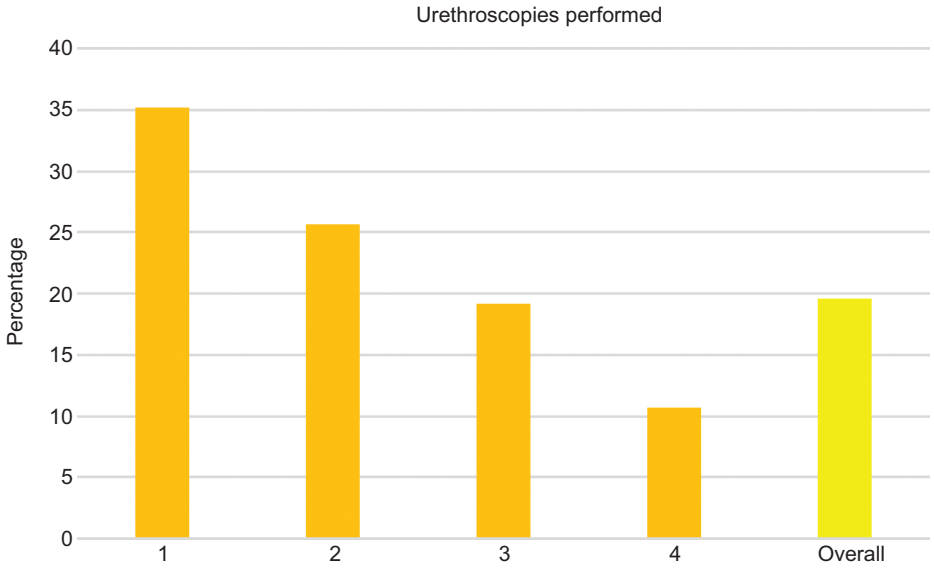

FIGURE 2 Surveillance rate. Bar graph demonstrating the percentage of patients undergoing 1, 2, 3 and 4 surveillance urethroscopies following RC (orange bars), and the overall percentage of patients who received appropriate urethral surveillance during the study period (yellow bar).

had urethral surveillance in keeping with the frequency suggested by NICE guidelines.

Mortality/OS

Over the study period, and of the 479 patients not discharged or having moved out of the area, 214 died. Eighteen patients died within 30 days of RC. From the data available, 13 patients died during the follow-up period due to reasons not directly linked to their bladder cancer; therefore, at 10 years (albeit with median 32 months follow up), disease-specific mortality was 42.0%, and overall or all-cause mortality was 44.7%.

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Urethral recurrence rate

Excluding the cases who had upfront urethrectomy and patients who underwent delayed urethrectomy for positive urethral margins, the overall UR rate (as detected by staging CT and/or urethroscopy) was 1.0% (n = 4). Two of these URs were detected on surveillance CT staging, and two were identified following non-routine investigations where patients were symptomatic: one with bleeding per urethra, and one with new onset penile or pelvic pain. No cases of UR were identified by routine or surveillance urethroscopy. All four cases of UR were found in patients with positive urethral margins after RC and did not undergo immediate urethrectomy.

DISCUSSION

Herein we present our regional 10-year retrospective data on urethral surveillance practices following RC. Our regional trainee-led research collaborative facilitated the collection of data from several centres and enabled inclusion of almost 500 cases. We have identified an overall poor adherence to national guidelines on urethral surveillance, and it is evident that the frequency, timing, and methods of surveillance used are heterogeneous between Trusts within the region, and indeed even within the Trusts themselves.

It is unclear why the urethral surveillance rate in our cohort was low, however, potential reasons include lack of familiarity with national guidance, the lack of perceived benefit of surveillance, the reliance on cross-sectional imaging as surveillance, the typically poor prognosis following RC and availability of resources. Furthermore, it is worth noting that National and European guidelines on urethral surveillance have changed in terminology over the study period (previously urethral washings were not recommended). Indeed, closer to the start of data collection, there were neither clear recommendations on time frame nor frequency over which urethral surveillance should be performed; even now, guidelines use the terminology "consider" (urethral surveillance) rather than, for example, suggest or recommend.[6] Whilst our rate of urethral surveillance is lower than many reports, it is comparable to several series described in a recent meta-analysis, where the authors noted the huge heterogeneity in surveillance protocols internationally.[9]

Although our observed rate of UR of 1% was lower than many previous studies, particularly the more historic ones, it was broadly in keeping with more recent reports.[8,9] Further supporting the reliability of our findings is the fact that majority of UR are identified in patients who present with symptoms such as penile and pelvic pain, urethral bleeding, and palpable urethral mass.[2,4,8] Given the clinic and radiological follow up in our patient cohort (half of our UR were identified on surveillance CT), it is unlikely that a significant number of UR were missed, although some asymptomatic UR may have remained undetected.

Notwithstanding, we accept that our low rate of surveillance urethroscopy and urethral washing cytology may well underestimate the true rate of UR in our region. Indeed, previous studies have suggested a three-fold increase in detection of UR when regular urethral wash cytology is used for surveillance, albeit these series found no differences in survival rates between follow up that included regular urethral cytology and follow up that did not.[11]

Therefore, although it is possible that our surveillance practices have underestimated the true regional UR rate, we must consider that the rate of UR we observed is accurate. This could reflect an inherent characteristic of our patient cohort and could suggest that the rate of UR is less than perhaps previously thought. Reasons for this may include the increased use of NACT, better stratification of high-risk NMIBC whereby RC is advocated for some patient risk groups that perhaps had previously been managed with intravesical therapies (BCG failure and HR-NMIBC progression are associated with worse outcomes than MIBC),[5,12,13] and the increasing age and comorbidity with which patients are being offered RC (reduced lifespan over which to find URs).[1] Although our study data cannot

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substantiate these possibilities, our cohort included many patients who received NACT and many were above the age of 80.

Nevertheless, what was clear from our series was that all patients we identified with UR were those that had positive urethral margins following RC. In these cases, it is unclear why urethrectomy was not performed upon finding positive margins, particularly when multiple previous reports describe positive urethral margins (alongside multifocal NMIBC and presence of CIS) as associated with greatest risk for development of UR (~50% cases).[4,9] Our data support the opinion that urethrectomy should be advocated in patients who are identified with positive urethral margins following RC. However, given our low UR rate, we were not able to evaluate associations with tumour factors in our patient cohort. We are therefore unable to confirm (in our patients) the previously identified high-risk groups for UR,[7,9,11,14] including patients with multifocal tumours and CIS, nor can we advocate upfront urethrectomy (concurrent with RC) for such patients based on our findings. Perhaps in these high-risk groups, and as it has been previously advocated,[3,12,14] bladder neck and/or prostatic urethral biopsy at time of trans urethral resection of bladder tumour can best guide the need for urethrectomy at time of RC.

In addition to lack of demonstrable patient benefit in our series, one must consider the potential disadvantages to performing routine urethral surveillance. These include the patients' hospital visits with attributable inconvenience and increased risks of exposure to coronavirus, the demands on surgeon, theatre and nursing staff and resources, and the costs of urethroscopy, urethral cytology and histopathologist time.

Although there are limitations to our study, including the retrospective nature and incomplete data for some cases that could introduce bias, our methodology and approach are similar to that of several previously published series.[3,4] Therefore, we have no reason to believe that our regional findings are significantly different from the national average. Indeed, our patient demographics, urethral surveillance practices, UR rate and disease-specific mortality are all comparable to previous reports and suggest that our data should be generalisable and could be indicative of nationally heterogeneous surveillance practice and poor adherence to NICE guidelines.

CONCLUSION

Our regional urethral surveillance practice following RC is heterogeneous and suboptimal in comparison to NICE guidelines. However, our UR rate was so low that we are unable to assert whether early detection (in an asymptomatic patient) has any clinical benefit. Based on our study data, we therefore do not advocate routine urethral surveillance, but suggest that patients with positive urethral margins should be offered immediate urethrectomy.

In addition, we advocate collaborative urological research and data collection to generate higher volume series, more representative and generalisable data, and more meaningful conclusions.

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