



ONCOLOGY/RECONSTRUCTION
ORIGINAL ARTICLE

Positive ureteric margins at radical cystectomy: Can it be predicted at initial transurethral resection of bladder tumour?

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Received 2 April 2018, Received in revised form 2 June 2018, Accepted 23 June 2018
Available online 14 July 2018

KEYWORDS

Bladder cancer;
Treatment;
Radical cystectomy;
Surgical margin;
Distal ureteric margin

ABBREVIATIONS

CIS, carcinoma *in situ*;
IFSA, intraoperative
frozen section analysis;
LVI, lymphovascular
invasion;
OR, odds ratio;

Abstract Objective: To identify primary tumour-related factors at transurethral resection of bladder tumour (TURBT) that may predict positive distal ureteric margins (PUM) at the time of radical cystectomy (RC).

Patients and methods: A retrospective, cohort study was conducted using our institution's data from June 2007 to June 2016. Patients who underwent TURBT followed by RC for non-metastatic urothelial carcinoma (UC) of the bladder were identified. In all, 211 patients underwent RC for UC during the study period. The patients were divided into two groups: Group-I ($n = 17$) with PUM and Group-II ($n = 194$) with negative ureteric margins. Univariate and multivariate analyses were performed to determine the predictors of PUM.

Results: On univariate analysis, multifocality, tumours involving the ureteric orifice, trigonal tumours, presence of carcinoma *in situ* (CIS), and lymphovascular invasion at TURBT, were significantly more common in Group-I. On multivariate analysis, tumour involvement in the ureteric orifice(s) and presence of associated CIS significantly predicted PUM.

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Peer review under responsibility of Arab Association of Urology.



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PUM, positive distal ureteric margins; TURBT, transurethral resection of bladder tumour; UC, urothelial carcinoma; UT, upper tract

Conclusions: Primary tumour-related factors on initial TURBT that predicted PUM (at RC) were involvement of the ureteric orifice(s) and presence of associated CIS. These results may help to select patients who can be selectively offered intraoperative frozen section analysis.

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Introduction

Historically, upper tract (UT) recurrence after radical cystectomy (RC) for urothelial carcinoma (UC) has been reported in 2–22% of cases [1–4] and these patients, due to multiple reasons, tend to have poorer prognosis compared to those with primary UT-UC [3,5–7]. Multiple tumour-related factors for UT recurrence have been identified including tumour grade, stage, multifocality, history of carcinoma *in situ* (CIS) in the RC specimen, prostatic urethral involvement, and the presence of distal ureteric involvement with CIS [1,8–13]. The incidence of positive distal ureteric margins (PUM) at RC ranges from 2% to 35% [14]. However, despite the fairly high incidence of PUM, the clinical significance of PUM at RC, as well as the role of intraoperative frozen section analysis (IFSA), is still under debate.

In our institute, we do not perform IFSA routinely, but rely on gross examination of the distal ureter. We planned to retrospectively analyse our data in order to identify tumour-related factors at initial transurethral resection of bladder tumour (TURBT) that would predict PUM, so that patients with risk factors may be selectively offered IFSA.

Patients and methods

Study design, setting and patients

After approval from the Institutional Review Board, we retrospectively reviewed the electronic record database of our institute from June 2007 to June 2016. Patients who underwent TURBT and subsequently RC for non-metastatic UC of the bladder were identified. The following variables were recorded: age; sex; history of use of tobacco; history of intravesical BCG or neoadjuvant chemotherapy; clinical TNM stage; presence of hydronephrosis; and primary pathological tumour features (on initial TURBT) including maximum size, multifocality, location in the bladder, stage and grade of tumour, presence of CIS, and/or other adverse histology. Patients with metastatic disease who underwent palliative RC, those with concomitant UT-UC or suspected to have UT-UC preoperatively were excluded. Data for 211 patients were available for analysis.

Surgical and pathological technique

Open RC with extended pelvic lymphadenectomy was performed according to the standard technique in all patients. Either an ileal conduit or ileal neobladder were performed for urinary diversion. The pros and cons of both options were discussed with the patients and the decision on the type of diversion was primarily influenced by the patient's age and comorbidities.

Most of the patients underwent an ileal conduit diversion, whilst only a few had an ileal neobladder. Ureters were transected at the level of or just below the iliac vessels, and visual assessment of the distal ureteric margins was carried out. IFSA was performed in only eight patients.

On histological examination of the RC specimen, ureteric margins were histologically classified as positive (involved) or negative (uninvolved). Ureteric margins with urothelial malignancy, CIS, high-grade atypia or dysplasia were classified as positive, i.e. PUM. This was correlated to the collected preoperative variables including pathological features of primary tumours at initial TURBT.

Statistical methods and analysis

All analyses were done using STATA 13.1/IC statistical software (Stata Corporation, College Station, TX, USA). Data were summarised as mean (SD) or median (range) for continuous variables, and frequency with percentage for categorical variables. For the purpose of analysis, we divided our cohort into two groups: Group-I comprised patients who had PUM, and the Group-II patients had negative distal ureteric margins. Both groups were compared for all the collected variables. Univariate relationships were studied using chi-squared statistics for categorical variables, and independent *t*-test/Mann–Whitney *U* test for continuous variables. Multivariate logistic regression was performed to examine the adjusted effects of different variables, so as to determine the predictors of PUM.

Results

Data from 211 patients who underwent TURBT and subsequently RC with ileal conduit (172 patients) or ileal neobladder (39 patients) for UC of bladder from

June 2007 to June 2016 were included in the analysis. Seventeen (8.1%) patients had PUM (Group-I), whilst 194 had negative ureteric margins (Group-II) on RC specimen. Both groups were comparable for age and sex distribution, although Group-I had significantly more patients with a history of tobacco use (Table 1). All patients in this cohort had high-grade UC on initial TURBT.

Of the 211 patients, 44 (20.8%) underwent RC for non-muscle-invasive bladder cancer. The majority of them had BCG-refractory cancer.

Both groups were similar in terms of mean maximum size of the tumour and presence of hydronephrosis. Multifocal tumours were more commonly associated with PUM than those with negative ureteric margins ($P = 0.04$). Patients with tumours involving the ureteric orifice and those located over the trigone were found to have a significantly greater chance of having PUM at final histology. A prior history of intravesical BCG or neoadjuvant chemotherapy was not found to be associated with PUM. Further analysis revealed that presence of CIS and lymphovascular invasion (LVI) at TURBT were significantly more common in Group-I. However, associated adverse histological features were equally distributed between the groups (Table 1).

On multivariate analysis, the factors that were found to be significant predictors of PUM included: history of tobacco use (odds ratio [OR] 12.90, 95% CI 10.6–15.2; $P = 0.003$), involvement of the ureteric orifice(s) by the tumour (OR 16.28, 95% CI 13.2–19.4; $P =$

0.001), and presence of associated CIS (OR 9.42, 95% CI 8.4–10.5; $P = 0.002$). After adjustment for other factors no associations were found for trigone involvement, multifocality and presence of LVI with PUM ($P > 0.1$) (Table 2).

In the present cohort, only eight patients underwent IFSA. All of them had gross involvement of ureteric orifice(s). Only two of them showed abnormality. One of them was converted to a negative ureteric margin after sequential sectioning and repeat IFSA. In the other case, an additional length of ureter was excised but further confirmation of a negative ureteric margin by repeat IFSA was not done. On final histology, the distal ureteric margin was negative in the first case; but revealed high-grade dysplasia in the second case. In the remaining six cases, distal ureteric margins were uninvolved on both IFSA and final histology.

Table 2 Multivariate analysis to determine the effect of various factors on PUM.

Factors	OR (95% CI)	<i>P</i>
History of smoking/tobacco use	12.90 (10.6–15.2)	0.003*
Involvement of the ureteric orifices	16.28 (13.2–19.4)	0.001*
Presence of CIS at TURBT	9.420 (8.4–10.5)	0.002*
Trigone involvement at TURBT	2.45 (1.35–3.55)	0.155
Presence of LVI at TURBT	1.37 (0.83–1.9)	0.763
Multifocal tumours at TURBT	0.66 (0.2–1.0)	0.88
Prior BCG	0.58 (0.3–0.8)	0.64
Hydronephrosis	0.97 (0.81–1.13)	0.531

* $P < 0.05$.

Table 1 Patients' demographic and tumour-related characteristics.

Variable	Group-I PUM	Group-II Negative ureteric margin	<i>P</i>
Number of patients	17	194	
Male: female	14: 3	176:18	0.73
Age, years			0.64
Mean (SD)	54.4 (11.5)	53 (10.1)	
Median (range)	51 (42–77)	55 (30–81)	0.54
Maximum size of tumour, cm, mean (SD)	5.8 (2.7)	5.11 (1.9)	0.71
<i>N</i> (%):			
History of smoking/tobacco use	13 (81)	107 (55)	0.015
Presence of hydronephrosis	9 (56.3)	86 (44.3)	0.36
Multifocal tumours	8 (47.0)	42 (21.6)	0.04*
Tumour involving the ureteric orifice(s)	14 (87.5)	74 (38.1)	0.002*
Trigone involvement	10 (58.8)	70 (36.1)	0.04*
Prior BCG or chemotherapy	1 (6.3)	40 (20.6)	0.19
Pathological stage and grade on TURBT			
pT1HG	4 (23.5)	59 (30.4)	0.43
pT2HG	10 (58.8)	127 (65.4)	0.48
pTaHG	3 (17.6)	8 (4.1)	0.034
Presence of CIS at TURBT	8 (47.0)	32 (16.5)	0.03*
Presence of LVI at TURBT	4 (23.5)	11 (5.7)	0.04*
Other adverse histology	7 (43.8)	56 (28.9)	0.35
– Sarcomatoid/squamous/glandular			

HG, high grade.

* $P < 0.05$.

Discussion

The incidence of UT recurrence after RC is quite low (3.4%) in most contemporary series [15]. PUM at RC and UT recurrence later are likely to be driven by adverse features related to the primary bladder lesion. The chances of UT recurrence after RC are higher if the distal ureteral margin is positive (especially if CIS is found) [11,16,17]. To reduce UT recurrences, IFSA was suggested, in order to detect PUM and ensure conversion to a negative ureteric margin. However, the routine use of IFSA in all patients during RC has been questioned. Although, IFSA can detect distal ureteric involvement with reasonable accuracy [11,18,19], high false-positive rates of up to 44% result in overestimation of disease at the distal ureteric margin [19]. Other issues associated with IFSA include practicality, cost-effectiveness, and increased operative time [20,21]. Thus, the risk–benefit ratio of routine IFSA is unlikely to be favourable, and a balanced and patient-specific implementation of IFSA is required.

However, risk factors for PUM and UT recurrence identified to date are based on final RC. Therefore, patients who have higher risk of PUM could be selectively offered IFSA if we can identify them based on primary tumour-related factors (at TURBT itself). If an abnormality is detected, the clinician may like to keep the patient on even more frequent screening. A recent study by Tollefson et al. [16] has shown that patients who undergo conversion to a negative final ureteric margin with IFSA and serial sectioning of the distal ureter have a reduced risk of UT recurrence. In their retrospective cohort of 1397 patients, IFSA was performed in all patients. Initial PUM was detected in 12.7%, and final resection PUM in 2.2% of patients. Amongst initial PUM, 82.6% were converted to a negative final margin. However, in a series by Gakis et al. [18] conversion to a negative final ureteric margin was not possible in > 50% of cases despite multiple re-resections.

Moschini et al. [22] have recently reported the only study to date (largest single centre European cohort, 1447 patients) that has shown that achieving negative ureteric margins by IFSA may be associated with survival benefit. However, this was seen amongst patients who had no residual cancer on RC specimen.

Almost all reported data related to the issue of distal ureteric margins are from series that incorporated IFSA. In the present series, ureteric transection was performed at the level of iliac vessels in all patients, and a routine IFSA was not performed. The PUM rate in the RC specimens was 8.1%. It is important that despite not performing routine IFSA in our present series, the incidence final PUM was low and similar to previous reports [19]. This indicates that further studies with larger number of patients are needed to clarify whether or not IFSA actually reduces final PUM. Nevertheless, our

present study identified primary tumour-related factors at TURBT, which predict PUM at RC and consequently patients could be selectively offered IFSA who might be benefited.

Our present study is retrospective with its attendant limitations. The number of patients in our present study was relatively fewer than in other studies. Further, it does not provide evidence for a relationship between PUM and UT recurrence. However, owing to the rare occurrence of PUM and even rarer that of UT recurrence, prospective studies with large numbers cannot be expected in near future.

Conclusions

The incidence of PUM following RC is low. On TURBT, the primary tumour-related factors that predicted PUM (at RC) in the present study were involvement of the ureteric orifice(s) by the tumour, and presence of associated CIS. Our present results may help to identify patients who can be selectively offered IFSA.

Source(s) of support

None.

Conflict of interest

None declared.

References

- [1] Johnson DE, Wishnow KI, Tenney D. Are frozen-section examinations of ureteral margins required for all patients undergoing radical cystectomy for bladder cancer? *Urology* 1989;**33**:451–4.
- [2] Huguet-Perez J, Palou J, Millan-Rodriguez F, Salvador-Bayarri J, Villavicencio-Mavrich H, Vicente-Rodriguez J. Upper tract transitional cell carcinoma following cystectomy for bladder cancer. *Eur Urol* 2001;**40**:318–23.
- [3] Zincke H, Garbeff PJ, Beahrs JR. Upper urinary tract transitional cell cancer after radical cystectomy for bladder cancer. *J Urol* 1984;**131**:50–2.
- [4] Nakanishi S, Nishiyama H, Ito M, Yoshimura K, Kamoto T, Ogawa O. Management of concomitant ureteral carcinoma in situ at radical cystectomy. *Int J Urol* 2006;**13**:524–8.
- [5] Balaji KC, McGuire M, Grotas J, Grimaldi G, Russo P. Upper tract recurrences following radical cystectomy: an analysis of prognostic factors, recurrence pattern and stage at presentation. *J Urol* 1999;**162**:1603–6.
- [6] Malkowicz SB, Skinner DG. Development of upper tract carcinoma after cystectomy for bladder carcinoma. *Urology* 1990;**36**:20–2.
- [7] Picozzi S, Ricci C, Gaeta M, Ratti D, Macchi A, Casellato S, et al. Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *J Urol* 2012;**188**:2046–54.
- [8] Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Huguet-Perez J, Vicente-Rodriguez J. Upper urinary tract tumors after primary superficial bladder tumors: prognostic factors and risk groups. *J Urol* 2000;**164**:1183–7.

- [9] Kenworthy P, Tanguay S, Dinney CP. The risk of upper tract recurrence following cystectomy in patients with transitional cell carcinoma involving the distal ureter. *J Urol* 1996;**155**:501–3.
- [10] Batista JE, Palou J, Iglesias J, Sancho E, da Luz P, Algaba F, et al. Significance of ureteral carcinoma in situ in specimens of cystectomy. *Eur Urol* 1994;**25**:313–5.
- [11] Raj GV, Tal R, Vickers A, Bochner BH, Serio A, Donat SM, et al. Significance of intraoperative ureteral evaluation at radical cystectomy for urothelial cancer. *Cancer* 2006;**107**:2167–72.
- [12] Sved PD, Gomez P, Nieder AM, Manoharan M, Kim SS, Soloway MS. Upper tract tumor after radical cystectomy for transitional cell carcinoma of the bladder: incidence and risk factors. *BJU Int* 2004;**94**:785–9.
- [13] Tran W, Serio AM, Raj GV, Dalbagni G, Vickers AJ, Bochner BH, et al. Longitudinal risk of upper tract recurrence following radical cystectomy for urothelial cancer and the potential implications for long-term surveillance. *J Urol* 2008;**179**:96–100.
- [14] Schumacher MC, Studer UE. Ureteric frozen sections during radical cystectomy for transitional cell carcinoma of the bladder – to do or not to do? *BJU Int* 2009;**103**:1149–50.
- [15] Donat SM. Staged based directed surveillance of invasive bladder cancer following radical cystectomy: valuable and effective? *World J Urol* 2006;**24**:557–64.
- [16] Tollefson MK, Blute ML, Farmer SA, Frank I. Significance of distal ureteral margin at radical cystectomy for urothelial carcinoma. *J Urol* 2010;**183**:81–6.
- [17] Schumacher MC, Scholz M, Weise ES, Fleischmann A, Thalmann GN, Studer UE. Is there an indication for frozen section examination of the ureteral margin during cystectomy for transitional cell carcinoma of the bladder? *J Urol* 2006;**176**:2409–13.
- [18] Gakis G, Schilling D, Perner S, Schwentner C, Sievert KD, Stenzl A. Sequential resection of malignant ureteral margins at radical cystectomy: a critical assessment of the value of frozen section analysis. *World J Urol* 2011;**29**:451–6.
- [19] Kim HS, Moon KC, Jeong CW, Kwak C, Kim HH, Ku JH. The clinical significance of intra-operative ureteral frozen section analysis at radical cystectomy for urothelial carcinoma of the bladder. *World J Urol* 2015;**33**:359–65.
- [20] Donat SM. Argument against frozen section analysis of distal ureters in transitional cell bladder cancer. *Nat Clin Pract Urol* 2008;**5**:538–9.
- [21] Satkunasivam R, Hu B, Metcalfe C, Ghodoussipour SB, Aron M, Cai J, et al. Utility and significance of ureteric frozen section analysis during radical cystectomy. *BJU Int* 2016;**117**:463–8.
- [22] Moschini M, Gallina A, Freschi M, Luzzago S, Fossati N, Gandaglia G, et al. Effect on postoperative survival of the status of distal ureteral margin: the necessity to achieve negative margins at the time of radical cystectomy. *Urol Oncol* 2016;**34**(59):e15–22.