Ureteral and urethral recurrence after radical cystectomy: a systematic review

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Purpose of review
The clinical significance of ureteral and urethral recurrence in patients treated with radical cystectomy for bladder cancer is scarce and heterogeneous. The aim of the current review is to summarize the recent literature on incidence, diagnosis and oncologic outcomes of ureteral and urethral recurrences after radical cystectomy.

Recent findings
Frozen section analysis (FSA) of ureteral margin had a sensitivity and specificity of 69–77 and 83–96%, respectively. Considering the ureteral margin, the reported sensitivity and specificity were 33–93 and 99–100%, respectively. Transurethral biopsy of the prostatic urethra might help in counseling patients' treatment, although its accuracy and prognostic role is highly questionable. In patients treated with radical cystectomy, recurrence of the urethra or ureteral are rare, occurring approximately in 5% of patients. During the follow-up, urinary cytology and cross-sectional imaging improve the early detection of recurrence in asymptomatic patients, although the majority are diagnosed for symptomatic presentation. Their use should be tailored to the patient's risk of ureteral and/or urethral recurrence. Urethrectomy is indicated in case of singular urethral recurrence, whereas no clear data exists regarding the best management of ureteral recurrence, except surgical removal.

Summary
Intraoperative FSA of ureters and urethra share good specificity but poor sensitivity. Recurrence at urethra and upper tract are rare and discordant data exists regarding survival outcomes. Oncologic surveillance after radical cystectomy with the aim to detect these recurrences should be tailored to the individualized patient's risk.

Keywords
bladder cancer, radical cystectomy, ureteral recurrence, urethral recurrence, urothelial carcinoma

INTRODUCTION

Radical cystectomy with bilateral pelvic lymphadenectomy is the standard of care for high-risk nonmuscle invasive and muscle-invasive bladder cancer (MIBC) [1–3]. Despite optimal treatment, between 40 and 60% of the patients will experience disease recurrence within 5 years and die of their disease eventually [4–6]. This high failure rate is likely because of undetected occult micrometastases at the time of radical cystectomy and genetic instability of the remaining urothelium [7–9]. Although systemic recurrence is more common, ureteral and urethral recurrences is seen in 4–10 and 1.3–13.7% of cases, respectively [10,11]. The life-long risk of recurrence in the remnant urothelium results in a close follow-up scheduling with often a challenging decision-making regarding further diagnostic interventions. To which degree ureteral or urethral recurrences affect survival is still unclear. Similarly, the management of such events is mostly based on case-series with low level of evidence.

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KEY POINTS

- Frozen section analysis of ureteral margin had a sensitivity and specificity of 69–77 and 83–96%, respectively.
- Considering the ureteral margin, the reported sensitivity and specificity were 33–93 and 99–100%, respectively.
- During the follow-up, urinary cytology and cross-sectional imaging improve the early detection of recurrences in asymptomatic patients.
- Detection and treatment of ureteral and urethral recurrences in asymptomatic patients may improve cancer-specific and overall mortality.
- Preoperative prostatic resection or biopsy does not improve decision-making or outcome significatively.

The aim of this systematic review is to summarize the current evidence on incidence, diagnosis and prognosis of ureteral and urethral recurrences after radical cystectomy, and to provide information for the management of these patients.

METHODS

A systematic literature review was performed in December 2019 using the Medline, Embase, and Web of Science databases. Review articles, editorials, and congress abstracts were excluded. Search terms included 'bladder cancer' in combination with the terms 'radical cystectomy' OR 'recurrence' OR 'frozen section' OR 'ureteral recurrence' OR 'urethral recurrence'. Only articles published in the last 10 years were considered (2009–2019). Previous published articles were included if considered relevant from the authors. The search was limited to the English literature. References cited in selected articles and in review articles retrieved in our search were also used to identify manuscripts that were not included in the initial search. The articles that provided the highest level of evidence were then evaluated. Whenever existing, prospective studies were preferred to retrospective designs. A list of articles judged to be highly relevant by the authors was circulated among the coauthors and a final consensus was reached on the structure of the review and the articles included. The systematic review was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] (Fig. 1).

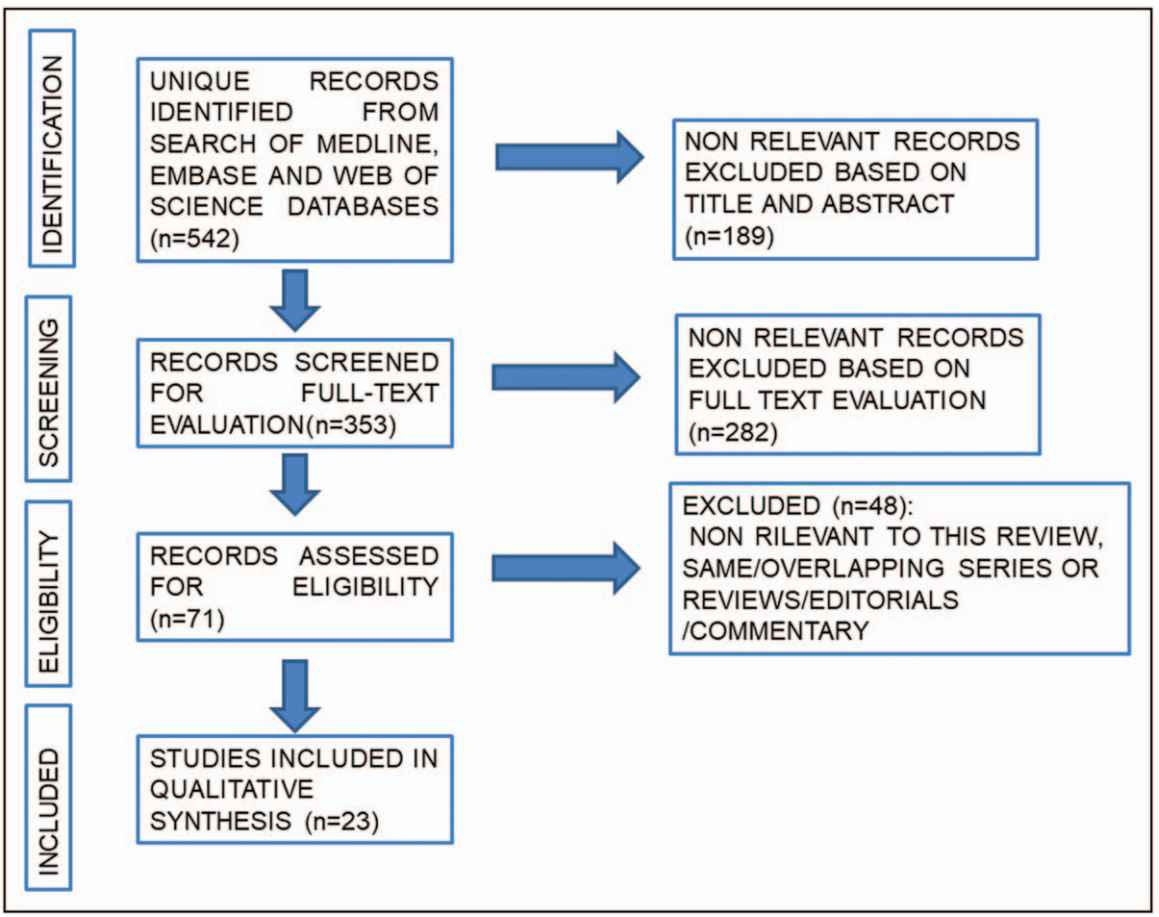

FIGURE 1. Flow diagram of the search results.

Table 1. Studies reporting results of frozen section during radical cystectomy

Reference	Patients, number	Positive ureteral margin (frozen)	Positive ureteral margin (final)	Sensitivity	Specificity	Ureteral recurrence	Association of positive ureteral margin with UUT recurrence	Impact on survival outcome
[15]	402	46, 11.2%	35, 8.7%	75	96	n.s.	n.s.	n.s.
[14]	1447	368, 25.4%	190, 13.1%	69	83	26 (7.1%)	n.s.	Hazard ratio 1.92, $P=0.01$[a]
[16]	2047	460, 22.4%	335, 16%	77	88	28, 1.4%	n.s.	n.s.
[17]	301	36, 12%	32, 11%	72	96	6, 2%	–	n.s.
[18]	98	9, 9%	–	–	–	–	–	Hazard ratio 4.2 $P=0.02$
[19]	218	17, 8%	23, 11%	74	98	–	–	–
[27]	298	26, 8.7%	15, 5%	100	99	–	–	Univariable: 1.75 (1.19–2.57) Multivariable: 1.65 (1.13–2.44)
[20]	458	30, 8.4	28, 6%	89	98	–	–	–
[21]	364	77, 10.1%	83, 10.9%	86	99	–	–	n.s.
[22]	1397	178, 12.7%	–	–	–	69, 4.9%	$P<0.001$	n.s.

CSS, cancer-specific survival; MVA, multivariable analysis; n.s., not significant ($P>0.05$); OS, overall survival.
[a]Only in patients with positive ureteral margin at final pathology, negative soft tissue margin and without node metastases.

PERIOPERATIVE EVALUATION OF URETERAL OR URETHRAL MARGIN IN RADICAL CYSTECTOMY CANDIDATES

The use of frozen section analysis (FSA) of the ureteric margin during radical cystectomy aims to identify and excise all malignant tissues, ultimately preventing local tumor recurrence at the anastomosis or in upper urinary tract. However, the accuracy and the prognostic benefit of this procedure is controversial [13–16]. Older series reported on an almost 1% false-negative rate [13]. In a retrospective series of 402 patients treated with radical cystectomy for urothelial carcinoma of the bladder (UCB), 46 (11.2%) patients had a positive ureteral margin on FSA with the diagnosis being confirmed on permanent section analysis in only 35 (8.7%) [15]. In a larger series of 1447 patients, an even higher rate of FSA was found with 25.4% of patients were also confirmation on permanent section analyses was in only 52% of the FSA-positive cases [14]. Satkunasivam *et al.* [16] expanded upon these findings by reporting the pathologic outcomes of 2047 patients treated with radical cystectomy for UCB at a single center institution between 1971 and 2009. Authors found pathologic ureteral margin at FSA in 31% and on permanent section analysis and in only 19.6% of the patients. In summary, these studies reported sensitivity and specificity of FSA between 69–77 and 83–96%, respectively [14–16]. A detailed overview of studies assessing FSA of the ureter is depicted in Table 1. It is still not clear what is the best therapeutic management of positive ureteral margin diagnosed at FSA during radical cystectomy with this suboptimal performance [17–22]. Although some authors perform a sequential removal of the ureter until finding a negative FSA, others suggest not to remove the ureter further because of the poor performance of the FSA and the unknown impact of the positive ureteral margin [14–16]. Indeed, although solid cancer may lead to recurrence, carcinoma *in situ* remains difficult to detect and its clinical significance is more heterogeneous. Patients at increased risk are those with extensive carcinoma *in situ* in the bladder [23], with hydronephrosis, with tumor of the ureter orifice, histological variants [24–26] or those with past history of upper tract tumor.

A detailed overview of studies assessing the value of FSA or preoperative biopsy of the urethra is depicted in Table 2. Similarly, for the ureteral margin, the reported sensitivity and specificity of urethral FSA is 33–93 and 99–100% [27–33], respectively. In 298 patients treated with radical cystectomy between 2000 and 2002, Kates *et al.* [27]. found positive urethral margin on FSA in 8.7% of patients, in half of them, a negative final margin was achievable after re-resection. All negative FSA during radical cystectomy were confirmed during final pathology analysis. On the basis of the high risk of local recurrence and the difficulty in early detection of such recurrence and its challenging management, FSA is performed at our institution in all cases of bladder and those at high risk of positive margin, such as those with prostatic involvement or suspicious imaging.

Table 2. Studies reporting results of urethral frozen section during radical cystectomy

Reference	Patients, number	Positive urethral margin (frozen)	Positive urethral margin (preoperative)	Positive urethral margin (final)	Sensitivity	Specificity
[27]	298	8.7%	–	7.8%	93%	100%
[28]	100	6%	–	5%	33.3%	98.8%
[31]	272	–	26%	2.2%	–	–
[32]	234	3%	34.6%	–	–	–
[33]	37	8%	–	–	–	–

Not only the intraoperative but also the preoperative endoscopic biopsy of the prostatic urethra has been suggested to help guide decision-making in select cases, particularly regarding sexual and continence-preserving techniques in male candidates for neobladders [1,34]. However, its accuracy and clinical value remain questionable. Gaya *et al*. [32] compared the accuracy of transurethral loop biopsy and cold cup biopsy with final pathology in 234 patients treated with radical cystectomy between 1990 and 2010. Overall, 81 (35%) of the patients had preoperative tumoral involvement of urethra. No differences were observed between the two techniques considering sensitivity and specificity. Fifty-two patients with preoperative positive biopsy were treated with urethrectomy at the time of radical cystectomy, 15 (29%) of them having a negative finding on final pathology. After a median follow-up of 30 months, only 1% of the patients with an intact urethra experienced an urethral recurrence. Although there may be a selection bias, the evidence does not support a need for preoperative assessment of the prostatic urethra in all patients. Taken together, the relatively poor accuracy of FSA for the detection of residual tumor in the ureters and urethra leaves the debate on its utility in clinical routine still open. A risk-based performance of FSA in select patients in whom it could affect further therapy may be a well tolerated approach.

INCIDENCE AND DIAGNOSIS OF URETERAL AND URETHRAL RECURRENCE DURING FOLLOW-UP

Recurrence in the remnant urothelium after radical cystectomy is rare occurring in about 5% of the cases [10,11,35]. International guidelines recommend an oncologic surveillance after radical cystectomy in order to identify early local and/or systemic disease recurrence [36]. However, the extension of surveillance protocols and whether the detection of symptomatic or asymptomatic recurrence impacts survival is still under debate [37,38]. A retrospective series of 1797 patients treated with radical cystectomy evaluated the accuracy of surveillance protocols recommended by current guidelines. Authors found that 98 (10.5%) patients had recurrence in the urethra and 87 (9.3%) in the upper urinary tract [39]. The National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) surveillance guidelines were particularly limited in patients with pT1 disease or less and would have detected only 36.8 and 77% of the upper tract recurrences, respectively [39]. On the basis of these findings, authors advocated an individualized surveillance protocol based on recurrence risk and competing health factors. Several pathologic features have been associated with upper tract recurrence after radical cystectomy. Due to diagnostic challenges of intraoperative FSA and the relatively low incidence of upper tract recurrence after radical cystectomy [35], current single-center retrospective series are probably underpowered. A meta-analysis of 13 185 patients [35] reported a upper tract recurrence rate after radical cystectomy between 0.75 and 6.4%. Recurrences occurred between 2.4 and 164 months after radical cystectomy. Although history of carcinoma *in situ*, solitary lesion, and type of diversion adopted were not associated with upper tract recurrence, authors identified recurrent bladder cancer and positive ureteral or urethral margins to be associated with upper tract recurrence. Interestingly, authors also found that patients with low grade [odds ratio (OR) 6.25] and nonmuscle-invasive tumors (OR 2.91) had a significantly higher risk of upper tract recurrence; probably because of their prolonged consecutive management and the genetic instability of these cases affecting the entire urothelium. In 62% of cases, a upper tract recurrence was diagnosed in symptomatic patients. In asymptomatic patients, instead, recurrence was diagnosed with upper tract imaging and urinary cytology in 30 and 7% of the cases, respectively. Considering urethral recurrence [11], incidence was reported to be approximately 4%, with significant lower incidence in patients receiving a neobladder diversion. This effect is probably because of preoperative selection bias. Presence

of muscle invasion at the definitive pathology analyses, carcinoma *in situ*, prostatic stromal involvement or prostatic urethral involvement were not associated with the risk of urethral recurrence during the follow-up period. An overview of the studies reporting incidence of upper tract and urethral recurrence after radical cystectomy is depicted in Table 3 [6,38,40–50].

The value of urinary cytology for the detection of upper tract [51–53] or urethra [38,54] recurrences has been widely investigated. Despite being an easy and noninvasive examination with a good predictive value, its use during surveillance can marginally improve the detection of recurrences before their clinical manifestation. Moreover, it has to be considered that this examination is highly investigator-dependent [55] and also given the relative low number of upper tract and urethra recurrences, up to 2000 urinary cytology examinations might be necessary to identify one recurrence [35]. This also affects the detection rates of cross-sectional imaging during the follow-up after radical cystectomy. Despite the ability to detect around 25% of asymptomatic recurrences, still 800 radiological examinations are needed to identify one upper tract recurrence [35]. Indeed, Labbate *et al.* [56] retrospectively reviewed clinical and pathological data of 357 patients who underwent radical cystectomy and orthotopic urinary diversion without intraoperative frozen section. During follow-up, six urethral recurrences were recorded; however, this occurrence was not higher in patients with a positive urethral margin ($P=0.2$). Moreover, urethral margin was not associated with differences in overall survival. The value of cytology and/or cystoscopy during follow-up after radical cystectomy to diagnose urethra recurrences was confirmed in a recent consensus paper [57,58].

The majority of patients are diagnosed with symptomatic recurrence during the follow-up after radical cystectomy [35]. Volkmer *et al.* [37] evaluated 1270 radical cystectomy for UCB performed at a single institution between 1986 and 2006. All patients had regular follow-up examinations. Overall, of the 444 patients who experienced a recurrence, 290 were symptomatic and occurred within a mean time after radical cystectomy of 17.5 months. However, no difference in survival between patients with symptomatic and asymptomatic recurrence could be observed. On the other hand, other studies found improved survival outcomes for recurrence diagnosed based on symptoms [38,59]. In contrast to these findings, Giannarini *et al.* [38] reported, in a retrospective series of 479 radical cystectomy patients, a significantly improved overall survival (hazard ratio 0.66) and cancer-specific survival (hazard ratio 0.65) if recurrence was diagnosed in asymptomatic patients. Recurrence in the remnant urothelium had a better prognosis compared with other recurrence sites. However, no subgroup analysis was reported. Boorjian *et al.* [59] analyzed 1599 patients treated with radical cystectomy between 1980 and 2000. During the follow-up, 38% of these patients developed a recurrence, 77% of those were symptomatic. They found that patients found with asymptomatic recurrence had a consistently improved survival outcomes compared with those diagnosed with symptomatic recurrence (hazard ratio 1.59, $P=0.0001$).

Upper tract recurrence seems to be not only dependent of pathologic characteristics of the tumor. Indeed, Kiss *et al.* [60] evaluated the association of ureteral stenting with the subsequent risk of developing upper tract. Authors analyzed 1005 patients treated with radical cystectomy between 2000 and 2016 at a single center. Overall, 11% of the patients received a drainage of the upper tract prior to radical cystectomy; specifically, 46% by double J stenting and 54% by percutaneous nephrostomy. Authors found that patients who received double J stenting were at higher risk of upper tract recurrence compared with patients who received percutaneous nephrostomy (hazard ratio 4.54, $P=0.01$). These data need to be confirmed in larger multicenter studies.

MANAGEMENT OF URETERAL AND URETHRAL RECURRENCE AFTER RADICAL CYSTECTOMY

Sparse data exists regarding the optimal management of upper tract recurrences. In the case of localized recurrence, surgical excision with segmental resection or radical nephroureterectomy should be considered [1].

Urethrectomy is considered the standard of care for urethral recurrence [1]. Only limited data exist regarding urethra-sparing strategies. Therefore, endocavitary chemotherapy, radiation therapy, BCG instillation or transurethral resection should be restricted to selected cases, such as noninvasive cases. Li *et al.* [61▪▪] evaluated, in a recent metanalyses, these urethra-sparing strategies. Data on 9498 patients treated with radical cystectomy were available. Overall, 14 studies evaluated the list of treatment and the impact of the treatments on survival outcomes of 272 urethral recurrences. Among these cases, 190 underwent urethrectomy, 52 urethra-sparing treatments, 17 transurethral resection, 2 penectomy and 1 emasculation. Considering differences between the studies, no definitive comparison between the type of treatment could be made,

Table 3. Studies reporting urethral or ureteral recurrence during follow up in patients treated with radical cystectomy because of bladder cancer

Reference	Patients, number	Follow-up, months, median	Urethral recurrence	Ureteral recurrence	Survival after recurrence	Salvage treatment
[40]	287	26	11 (3.8%)	–	No difference between CSS for patients with or without urethral recurrence	Two patients Urethrectomy 4 patients local RT3 patients systemic chemotherapy
[41]	1506	13	85 (5.6%)	–	5 years CSSCytology: 80%Symptoms: 41%	95 patients urethrectomy
[42]	282	56	1.4% female 3.3% male	–	5-year CSS higher in patients with urethral recurrence alone (83.3%), compared with patients with other recurrences	Transurethral resection of tumour, urethrectomy, neobladder resection, revision of urinary diversion, adjuvant chemotherapy, or radiation therapy
[43]	1420	58	–	25, 5, 10, 15 years were 2.4, 3.9 and 4.9%	44% CSS survival at 24 months	–
[44]	297	64	7 (2.1%)	–	–	–
[38]	479	52	24, 5%	2.9%	6 (46%) are still alive with no evidence of disease after a median observation time of 6.2 years from radical cystectomy.	12 (92%) urethra-sparing treatment (i.e. endourethral BCG)
[45]	1388	186	–	67,	–	–
[46]	1797	126	98	87	–	–
[47]	2029	144	55	25	Urothelial recurrence within 2 years of radical cystectomy had a lower post recurrence disease specific ($P = .002$) and overall survival ($P = .003$)	–
[6]	1110	78	8	11	Secondary urothelial not associated with worse survival than local (but better than distant)	–
[48]	574	45	18, 3.6	21, 3.7	OS at 10 years 43% for UTUC recurrence, 66% for those with UR and 68% for patients without any recurrences.	–
[49]	260	62	6,2.3	–	Four of these six patients were alive without disease, one was alive with disease, and one had died from disease.	Transurethral resection, urethrectomy with conversion of neobladder to continent catheterizable diversion, and chemotherapy
[50]	362	48	–	11, 3%	The median overall survival period after upper urinary tract recurrence was 23.5 months (range 4.3–53.9)	–

CSS, cancer-specific survival; MVA, multivariable analysis; n.s., not significant ($P > 0.05$); OS, overall survival.

suggesting that new research is needed to find the optimal management of urethral recurrence.

CONCLUSION

Intraoperative FSA of ureters and urethra have a good specificity but a poor sensitivity. In select high-risk cases, they may help to change the management during surgery. Although transurethral biopsy of the prostatic urethra prior to radical cystectomy has been suggested to help in counselling regarding diversion type and nerve-sparing approaches, its accuracy and prognostic role is highly questionable. Upper tract and urethral recurrence are rare with discordant data existing regarding their individual impact on survival outcomes. Oncologic surveillance after radical cystectomy with the aim to detect these recurrences should be tailored to the individualized patient's risk. Despite the challenges of urethral and ureteral management, optimization of these frontiers may help improve radical cystectomy functional and oncologic outcomes to reach more acceptable rates.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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