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Achieving disease free distal ureteral margin at the time of radical cystectomy: Why and for whom? (an overview of literature)

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Achieving disease free distal ureteral margin at the time of radical cystectomy: Why and for whom? (an overview of literature)

Introduction

Radical cystectomy (RC) with pelvic lymph node dissection is the standard treatment option for non-metastatic, resectable muscle invasive bladder cancer (BCa) with a life expectancy rate close to 70 % at 5 years [1]. However, in order to maximize oncologic outcome, the surgical procedure has to be standardized [2]. Patients with BCa are at risk of experiencing upper urinary tract recurrences (UUTR) during the follow-up period [3]. Upper urinary tract recurrence is frequently symptomatic, advanced disease, and associated with a metastatic evolution that severely affect survival expectancy [3,4,5].

Although patients with a positive ureteral intraoperative frozen section have been found to be at increased risk of developing UUTR during follow-up [6,7,8,9], the optimal intraoperative management of patients with intraoperative positive ureteral margin is still under debate. Surgeons make the decision to evaluate margins intraoperatively on a case-by-case basis. Analysis of available literature questions both: 1/ the ability of intra operative frozen sections to properly predict final involvement of the ureters; 2/ the impact of invaded intra operative ureteral sections (with or without achieving negative ureteral margin) on upper urinary tract recurrences and oncological outcome; 3/ patients most likely to benefit of intra operative ureteral frozen section. In that regard, the latest EAU guidelines do not provide any recommendations [2]. The aim of this review was to evaluate frequency, reliability and impact of positive distal ureteral margin after radical cystectomy for bladder cancer on upper tract recurrence, cancer specific and overall survival, and to identify best candidates for intra operative frozen section analyses.

Material and Methods

A systemic review was performed following the PRISMA guideline using PubMed/Medline and Cochrane Library databases to identify eligible studies published between the creation of the databases and April 2020. The primary search string included the following items: bladder cancer OR cystectomy AND frozen section OR ureteral margin. Filters were applied to exclude any studies not performed on humans. Additionally, a manual search of the reference lists of relevant meta-analysis was conducted to identify all available studies.

The reference lists from selected papers were also searched for relevant studies that may have been missed during the initial searches. Papers for inclusion analyzed at patient treated by radical cystectomy for urothelial carcinoma of the bladder (Bladder cancer, BCa). The papers studied ureteral margin, prognostic factors associated with positive ureteral margin and their conversion to negative, and evaluated impact on upper urinary tract recurrence-free rate (UUTR), cancer-specific survival, and overall survival of these positive ureteral margins. Randomized controlled trials and prospective or retrospective analyses exploring patients with BCa treated by RC and studied on the basis of ureteral margin have been included. All previous reviews were automatically excluded, as were single case reports, editorial pieces, comment, and titles that were not available in English/French. The subsequently available papers were then systematically reviewed. The ultimate goal of this review was to assess any available papers that examined ureteral margin status at time of RC (frozen (FS) and permanent sections (PS)), that identified prognostic factors associated with positive ureteral margins, and that evaluated impact on upper urinary tract recurrence-free rate (UUTR), Cancer-Specific Survival (CSS), and Overall Survival (OS). The search technique is summarized in Figure 1.

Results

In total, thirty two relevant studies were identified. All studies published between 1989 and 2020 were retrospective, except the one published by Osman *et al*. [7]. Of these, seventeen studies reported specifically ureteral margin status (Table 1), and seventeen studies have recorded reliability of FS using PS as a reference (Table 2). Furthermore, twelve studies reported ureteral margin status (FS and/or PS) and upper urinary tract recurrence risk and three studies evaluated distal ureteral margin status as prognostic factor for cancer specific or overall survival after cystectomy (Table 3). Twelve studies explored prognostic factors associated with pathological positive ureteral margin at time of RC (Table 4). Potential studies bias have been reported Table 5.

Positive frozen section (FS) and permanent section (PS) rate

In contemporary series, the incidence of initial positive ureteral margin ranged between 1.1% to 25.4% for FS, and between 0.8% and 15% for PS (Table 1) [6-22]. Sensibility ranged from 45 to 100% and specificity from 83 to 100%. Positive Predictive Value (PPV) ranged from 25 to 100% and Negative Predictive Value (NPV) from 91 to 100%. Positive margin was successfully converted to negative margin during surgery for 39% to 100% patients (Table 2) [6-9,12,13,15,16,18-26].

Positive ureteral margins and upper urinary tract recurrence (UUTR), cancer specific and overall survival.

After total cystectomy, Upper Urinary Tract Recurrence (UUTR) is an uncommon event and was recorded for 0.2% to 6.2% of patients (Table 3) [6,8,9,10,12,13,15,19-22]. Positive section was associated with higher rate of UUTR [6,8,9,21,22]. However, intraoperative positive frozen section converted to negative was associated with lower risk of UUTR compared to non-converted [8, 9, 21, 22].

In some papers, specific attention was paid to discriminate specific incidence of invasive tumor in uretero-ileal anastomosis from UUTR. Anastomotic recurrence was

uncommon and its occurrence ranged between 0% and 1% (Table 3) [6,8-10,12,13,15,16,19,22].

Regarding association with cancer specific mortality, results are equivocal. Cancer specific mortality attributable to concomitant carcinoma in situ on ureteral section appeared to be weak, probably hidden by bladder cancer specific mortality. Two contemporary retrospective studies (with more than 300 patients) failed to associate positive frozen section to survival [16,20], while Moschini *et al* associated positive frozen section with CSS and OS in one of the largest retrospective study published (n=1147)[21].

Prognostic factors associated with positive ureteral margins

Eleven studies reported prognostic factors associated with positive ureteral sections. All but one included a multivariate analysis. No prospective study was identified. Involvement of the prostatic urethra, history of bladder Cis, trigone involvement, hydronephrosis, clinical stage over pT2, tumor multifocality were advocated [6,7,9,16-19,21,22,24,27,28] (Table 4). Bladder CIS was the most consistent factor associated with positive ureteral section (FS and/or PS) at time of radical cystectomy (odds ratio between 6.4 and 177.9 for FS and between 3.3 and 11.1 for PS (Table 4)).

Discussion

To our knowledge, this study is the first systemic extended review related to ureteral margin frequency, reliability and impact of positive distal ureteral margin on upper tract recurrence, cancer specific and overall survival. This systemic review have shown a significant degree of clinical and methodological heterogeneity across all studies (including patient groups, length of follow up and outcome measures), preventing pooled analysis of the results and making direct comparison between the papers sometime very challenging. Furthermore quality of these reports did not meet current standards of evidence-based medecine and were most of the time based on retrospective studies (Level 4).

Positive frozen section rate

Performing frozen section analysis of the distal ureteral margins at the time of cystectomy is daily routine in many urologic institutions. Positive results would lead to additional tissue resection in order to obtain a negative margin status. In old series, assiduous approaches using step-sectioning techniques have demonstrated that more than half of patients showed intra epithelial carcinoma or more advanced ureteric lesions for solid papillary bladder tumors, and more than one third showed carcinoma in situ or more advanced lesions in the ureteric stumps [29,30].

In contemporary series, we observed a high variability in the positive ureteral section rate (1.1% to 25.4%) [6-22]. It can be explained as much by some differences in pathologic evaluation and definition of ureteral sample (presence of carcinoma and CIS for most of the authors, associated with high grade dysplasia and atypia for others), as well as by differences in intraoperative management of ureteral length (shortening of the ureter probably minimizes the risk of positive surgical margins). Hence when the redundant ureter segment resected above the common iliac vessels was performed, carcinoma in situ was detected in only 0.1%

on permanent section, suggesting that ureteral frozen section analysis is probably unnecessary in the majority of patients undergoing RC [15].

Sensibility and specificity of ureteral frozen section (FS)

Despite the risk of distal ureteric malignancy on radical cystectomy specimen [15], the clinical value of routine FS remains questionable. Studies reported in this review showed that FS confirmed a very good specificity and a very good NPV [6,9,13,16,18,20,22,24,25]. Using "presence of carcinoma" as pathologic definition of ureteral sample increased the specificity without large compromises in sensitivity [20]. However, with its low positive predictive value, FS tends to underestimate disease at the ureteral margin [7,13,16].

From a surgical point of view: indeed, there is no detrimental effect of performing FS (it is not time consuming). However in case of resection of the redundant ureter segment above the common iliac vessels, some authors reported that carcinoma in situ was not detected for 99.9% patients on permanent section, suggesting that ureteral frozen section analysis is probably unnecessary in the majority of patients undergoing RC. One may consider that resecting 5 cm or 10 cm (to be above the common iliac vessels) doesn't take much more time to surgeons than performing FS. Moreover, this technical point should be useful to avoid damage inflicted on the ureter during distal surgical mobilization, and subsequent complications such as necrosis and stenosis. From a cost-effectiveness point of view, the direct and indirect costs associated with FS are substantial and should be considered given the questionable clinical value of this test. Therefore, for some authors FS should be advocated and performed for selected patients undergoing radical cystectomy [16]. From a Human Resources point of view, access conditions to FS are somewhat heterogeneous in terms of hospitalization structure and execution (e.g. Cryostat, Décimu), making the availability of this examination sometimes difficult.

Positive ureteral margins (PUM) and upper urinary tract recurrence (UUTR), cancer specific and overall survival.

Several retrospective studies have shown that a positive ureteral margin does predict upper urinary tract recurrence [6,8,15,22,24,31] and may be associated with malignant ureteroenteric stricture occurring in approximately 0.2% to 1% [14,32] of the cases. For Schumacher *et al.* when frozen sections were negative, 3% of patients developed UUTR, vs.17% when frozen sections were positive [15]. However, frequency of UUTR was probably linked to differences in intraoperative management performed by surgeons, and when the redundant ureteral segment was resected above the common iliac vessels, UUTR was detected in only 0.3% of patients [15]. Moreover, recurrence side did not always match with the positive ureteral section side [6,8,14,20].

Consequently, intraoperative analysis of ureteral margin should theoretically facilitate tumor removal, decrease upper urinary tract recurrence (UUTR) rate and improve cancer specific survival. On a practical level, in many cases, an initial positive margin on frozen section can be converted to a final negative margin by sequential sectioning of the ureter (more than 50% of cases) [7,12,13,15,16,18,19,20,22,23,25,26], even if for some authors sequential ureteral resection was associated with low intraoperative conversion rates[6,9].

So far, there is no definitive evidence that complete extirpation of malignant ureteric involvement (proven by negative frozen sections margin during RC) eliminates the risk for recurrence of UUT disease [4-6,15,33,34] even if conversion from positive FS to negative FS, and/or negative PS, may improve UUTR free status in several retrospective studies [8,9, 21,22].

Indeed, pagetoid spread of CIS makes it is impossible to guarantee that negative frozen sections ensure that CIS is not more proximal. Some data support the theory that, in addition to local field progression of the disease, a multicentric process is involved in the

etiology of UUTR (due to intraluminal seeding and intraepithelial migration). Such hypothesis is also consistent with the fact that, in patients with bladder cancer CIS, upper tract involvement is associated with high rate of prostate involvement (67.6%) and bilateral ureteral disease (32%) [35]. Because urothelial carcinoma is associated with pan epithelial field defect and skip lesions are more common in patients with bladder CIS, tumor may occur anywhere in the urinary tract after treating an initial carcinoma [25]. Hoang *et al*. analyzed 660 patients who underwent RC and found 4.8% of ureteric skip lesion, half of them related to CIS [25]. Then, positive ureteral surgical margin did not necessarily translate to a large impact on patient outcome, and the risk of UUTR remained difficult to be evaluated (small cohorts, short follow-ups and competing risk with dying from bladder cancer) [5,6,31,36].

As for UUTR, it remains controversial if clearing the margins improves cancer survival. Given the low number of upper tract recurrences and the weak association between such recurrences and death, it is unlikely to have a significant impact on reducing recurrences on cancer specific survival and overall survival outcome. Various groups suggested that ureteral carcinoma in situ in ureteral surgical margin barely contributes to cancer specific survival and overall mortality in patients who undergo radical cystectomy [8,12,14,16,20,22]. Only one large retrospective study, published by Moschini *et al.* reported the beneficial effect of sequential sectioning FS on cancer specific survival and overall survival, only for patients who were found N0, R0, and <pT3 [21].

Prognostic factors for positive ureteral margins

Targeting the high-risk subgroups for positive margins could confirm the utility, the clinical significance and the impact on UUTR, cancer specific survival and overall survival of FS at time of radical cystectomy (RC).

Based on step-sectioning, radical cystectomy specimen was associated with grade 3 carcinomas mucosal involvement (CIS and high grade dysplasia) adjacent to and remote from

the visible tumor for 30 to 50% of patients [30,37]. Trigone region and contiguous posterior wall were particularly affected, and 57.1% patients were concerned by ureteral involvement (demonstrating direct intramucosal spread of malignant epithelial cells process) [30]. Finding published by Johnson *et al*. and Schumacher *et al.* suggested that patients with CIS of the bladder can have concomitant CIS of the distal ureter, in as many as 24% of patients [10,15].

Long ago, Johnson *et al* emphasized the importance of careful examination of the ureteral margin prior to constructing ureteroenteric anastomoses in patients with multifocal carcinoma in situ involving either the bladder or prostatic ducts [10]. Two contemporary studies with low numbers of patients [7,17] and with low frequency CIS within the bladder (20% and 27.7% respectively) [17,22], showed no association with positive ureteral margin [7,17,22]. However, even if some problem for histopathological diagnosis may exist, in several retrospective recent studies, ureteral CIS involvement was significantly associated with the presence of the CIS within the bladder [6,16,18,19,21,24,27,28].

Schumacher *et al*. reported that close to 80% of patients with CIS in the ureter have CIS in the bladder [15], and Raj *et al*. reported 30% of patients with bladder CIS have ureteric involvement in the RC versus only 9% of patients without [6]. Unfortunately, the presence of CIS in TURBT and RC specimens was also predictive and correlated with ureteric skip lesion (odds ratio [OR] 4.15, 95% CI 2.00-8.55, $p<0.001$) and [OR] 7.87, 95%CI 3.19-19.23, $p<0.001$], respectively [25].

Due to the retrospective nature of studies, we were unable to determine whether CIS was focal or diffuse and if the extent of CIS was associated with an altered risk of ureteral involvement, upper recurrence or survival outcomes. However, factors associated with an increasing risk ratio for UUTR, included history of CIS, history of recurrent bladder cancer, cystectomy for noninvasive bladder cancer [3, 35]. Typically, Cis is present in close to 10% of TUR specimens versus 30 to 50% after cystectomy and final examination. This can be

explained by the fact that less material was analyzed during TUR and by the difficulty and dedication required to determine the presence of concomitant Cis at the morphologic level (inter observer variability). However some qualitative concepts, associated with adherence to specific National and International guideline, must be reminded to really rely on TUR specimen [2]. Initial treatment for bladder cancer involves transurethral resection (TUR) of tumors to remove all possible tumors and obtain material for histological examination. As a result, resection patients are started on treatment pathways that reflect the nature and the potential of their disease. If TUR should include a deeper part, which has to be sent in separately, incomplete TUR should be exceptional (technical considerations) to avoid re-TUR necessity (morbidity and cost implication) and to reflect as close as possible the nature of the disease. Additional bladder biopsy should be associated for bladder abnormal-looking urothelium and when cytology is positive and when a non-papillary appearance was found. In the 21st century (equipment shall be available), photodynamic diagnosis could be considered to identify associated carcinoma in situ (Cis), and since the presence of Cis may lead to a modified treatment plan (eg. chemo radiation) [2].

In orphan retrospective studies, other prognostic factors were discussed like tumor location (trigone), tumor multifocality, clinical stage, number of tumor, intramural invasion, mucosal or ductal prostatic urothelial cancer, and hydronephrosis [9,17,19,22,28].

Studies limitations

Most of the results published were derived from retrospective, observational data. Due to several limitations like patient-selection factors, surgical technique, multiplicity of surgeons, frequency follow-up, neoadjuvant chemotherapy before RC, imaging modalities used - which improved during last decade, and limited number of UUTR, the statistical relevance should be questioned. In retrospective studies, potential errors introduced by incomplete data acquisition and patient selection bias should be discussed [17]. In context,

differences in survival recorded in the subgroup of patients with negative soft tissue margins and negative node metastases could be an indirect effect of uncontrolled factors [21].

Conclusion

Literature data suggest that ureteral frozen section analysis is probably unnecessary in the majority of patients undergoing RC, and even more so when the redundant ureteral segment was resected above the common iliac vessels. For patients with CIS within the bladder, frozen section (FS) at the time of RC can accurately detect ureteral involvement with reliable specificity.

Several retrospective studies have shown that conversion from positive FS to negative may improve UUTR free status. Only one retrospective study showed the beneficial effect of sequential sectioning FS on cancer specific survival and overall survival only for patients (<pT3, R0, N0).

Adequate powered randomized controlled trial, based on large structured collaborative studies, are necessary to confirm the clinical significance and utility (UUTR, Cancer Specific Survival and Overall Survival) of FS at time of radical cystectomy.

Legends

Figure 1. PRISMA flow diagram

Table 1. Studies reporting ureteral margin status.

Table 2. Reliability of Frozen section using permanent section as a reference (PPV: positive predictive value; NPV: negative predictive value; FS: frozen section).

Table 3. Studies reporting ureteral margin status and upper urinary tract recurrence (UUTR), Cancer Specific Survival (CSS) and Overall Survival (OS).

Table 4. Predicting pathological positive ureteral margin at time of RC (FS: frozen section; PS: permanent section).

Table 5. Potentially associated biases (IVP: intravenous pyelogram; CTS: computerized tomographic scan).

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Figure 1.

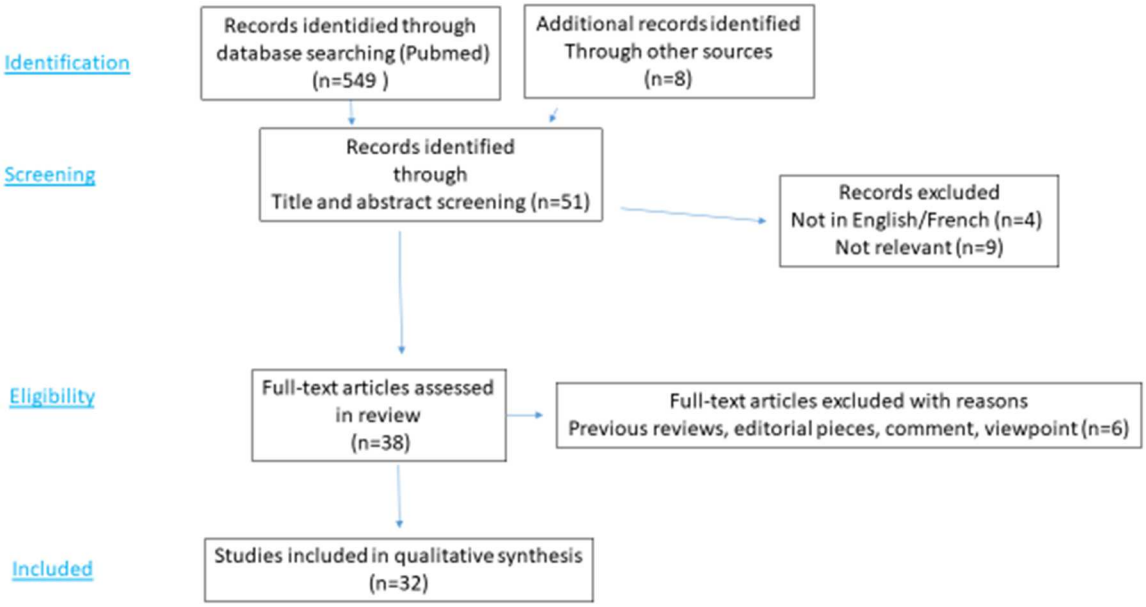
Identification
Records identidied through database searching (Pubmed) (n=549)
Additional records identified Through other sources (n=8)
Screening
Records identified through Title and abstract screening (n=51)
Records excluded
Not in English/French (n=4)
Not relevant (n=9)
Eligibility
Full-text articles assessed in review (n=38)
Full-text articles excluded with reasons
Previous reviews, editorial pieces, comment, viewpoint (n=6)
Included
Studies included in qualitative synthesis (n=32)

Table 1.

Author [Reference]	Year of publication	Type of study	Follow-up Mean (Median) [-] months	Number of patients studied (n)	% of patients with positive ureteral margins Frozen section (FS) % (n)	% of patients with positive ureteral margin Permanent section (PS) % (n)	Definition Histologic finding
Johnson *et al.* [10]	1989	Retrospective	24 [8-66]	n=403	2% (8/403) 7,2% (29/403)	- -	Ta,T1,CIS Ta,T1,CIS, Dysplasia
Batista *et al.* [11]	1994	Retrospective	24.5 [4-72]	n=242	-	5.7% (14/242)	CIS
Schoenberg *et al.* [12]	1996	Retrospective	67 [3-148]	n=97	8.2% (8/97)	12.3% (12/97)	All carcinoma, CIS, mild atypia to severe atypia
Silver *et al.* [13]	1997	Retrospective	31.8 (22.9) [2-74.2]	n=401	6.2% (25/401)	5.2% (21/401)	Carcinoma, CIS
Lee *et al.* [14]	2006	Retrospective	(37.1) [2-113]	n=115	-	4.3% (5/115)	CIS
Schumacher *et al.* [15]	2006	Retrospective	(30) [2-96]	n=805	4.8% (39/805) . 1.1% (9/805) TCC . 3.7% (30/805) Cis . 1.4% (11/805) Severe atypia	. 0.8% (7/805) TCC . 2.7% (22/805) Cis	All carcinoma, CIS, Severe Atypia
Raj *et al*. [6]	2006	Retrospective	(38.4) [1.2-204]	n=1330	10% * (124/1217) (*) ureter unit	13% (171/1330) 9% * (222/2579) (*) ureter unit	All carcinoma, CIS High grade atypia or dysplasia
Osman *et al.* [7]	2006	Prospective	-	n=100	14% (14/100) 8% * (16/ 193) (*) ureter unit	24% (24/100) 15% * (29 /193) (*) ureter unit	All carcinoma, CIS
Tollefson *et al.* [8]	2010	Retrospective	(43.2) [0.1-337.2] Patients dead (168) [0.4349.2) Patients alive	n=1397	12.7% (178/1378)	-	All carcinoma, CIS High grade atypia or dysplasia
Touma *et al.* [16]	2010	Retrospective	31.3	n=301	2.8% * (10/362) (*) ureter unit	8.8%* (32/362) (*) ureter unit	All carcinoma, CIS
Gakis *et al.* [9]	2011	Retrospective	(24) [1-116]	n=218	6.9% (15/218) 4%* (17/425) (*) ureter unit	9.2% (20/218) 5.2% *(23/425 (*) ureter unit	All carcinoma, CIS
Gondo *et al.* [17]	2013	Retrospective	-	n=197	19.3%* (38/197) (*) positive ureteral involvement (FS and/or PS)	-	All carcinoma, CIS
Zhou *et al.* [18]	2014	Retrospective	-	n=203	8.4% (17/203)	-	All carcinoma, CIS
Kim *et al.* [19]	2015	Retrospective	-	n=402	11.5% (46/402)	8.7% (35)	All carcinoma, CIS, atypia, dysplasia
Reder *et al.* [20]	2015	Retrospective	(26) [0-156]	n=364	6.3% *(48/768) Cis 3.8% *(29/768) carcinoma (*) ureter unit	7.2%*(55/768) Cis 3.7%*(28/768) carcinoma (*) ureter unit	All carcinoma,CIS
Moschini *et al.* [21]	2016	Retrospective	95 (102)	n=1447	25.4% (368/1447)	13.1% (190/1447)	All carcinoma, CIS, high grade atypia
Satkunasivam *et al.* [22]	2016	Retrospective	(12.4) [1.9-10.1]	n=2047	8.6% (178/2047)	3.2% (66/2047)	All carcinoma, CIS, Severe atypia

Table 2.

Authors [Reference]	Year of publication	Sensibility	Specificity	PPV	NPP	% positive FS converted to negative
Schoenberg *et al.* [12]	1996	50%	97.6%	75%	93.2%	50%
Silver *et al.* [13]	1996	75%	97.4%	60%	98.6%	50%
Schumacher *et al.* [15]	2006	-	-	-	-	55.6% for TCC 96.7% for CIS
Raj *et al.* [6]	2006	73.7%	98.9%	90.3%	96.3%	39%
Osman *et al.* [7]	2006	45%	98%	81%	91%	100%
Tollefson *et al.* [8]	2010	-	-	-	-	82.6%
Touma *et al.* [16]	2010	71.9%	96.1%	63.9%	97.2%	-
Gakis *et al.* [9]	2011	73.9%	99.8%	94.4%	98.5%	41.1%
Gordetsky *et al.* [23]	2014	-	-	-	-	52.5%
Loeser *et al.* [24]	2014	-	-	100%	98%	-
Hoang *et al.* [25]	2014	80% (without skip lesions) 22% (with skip lesions)	95% (without skip lesion) 89% (with skip lesions)	25% (without skip lesion) 62.5% (with skip lesions)	99.5% (without skip lesion) 54.5% (with skip lesions)	-
Zhou *et al.* [18]	2014	100%	100%	100%	100	-
Kim *et al.* [19]	2014	75% 69% (CIS and carcinoma only)	96% 99%	55.5% 96%	98.3% 98.2%	75.6%
Reder *et al.* [20]	2015	82% (severe dysplasia/CIS) 86% (carcinoma only)	99% 99%	88% 89%	98% 99%	-
Moschini *et al.* [21]	2016	69%	83%	-	-	48%
Satkunasivam *et al.* [22]	2016	59.1%	93%	-	-	66.4%
Cerf *et al.* [26]	2020	91.5%	100%	100%	98.4%	74%

Table 3.

Authors [Ref]	Year of publication (n)	% (n) of patients with FS(+)	% (n) of patients tumor free after new section	% of patients (n) with Upper urinary tract recurrence (UUTR)	% of patients (n) Ureteroenteric site recurrence (UER)	Upper urinary tract recurrence free rates according to the first and final margin ureteral status
Johnson *et al.* [10]	1989 (n=403)	2% (8/403)	17% (1/6)	0.2% (1/403) dysplasia on FS	0%	-
Schoenberg *et al.* [12]	1996 (n=97)	8.2% (8/97)	50%	1% (1/97) (Cis on PS)	0%	-
Silver *et al.* [13]	1997 (n=401)	6.2% (25/401)	50%	0.5% (2/401)	0.25% (1/401)	-
Schumacher *et al.* [15]	2006 (n=805)	3.5% (29/805)	55,6% for TCC 96,7% for Cis	3.9% (31/805)	0.25% (2/805) (1 with CIS on frozen section)	-
Raj *et al.* [6]	2006 (n=1330)	13% (171/1330)	39%	6.2% (82/1330)	1% (13/1330) . *2/13 PS(+) at anastomosis (1.3%. 2/156) . *11/13 PS(-) at anastomosis (0.5% ; 11/2423) (*) ureter unit	PS(+) was associated with UUTR HR 1.8 ; 95% CI, 1.1-3.1 (p=0.04) PS(+) was not associated with UER (p=0.2)
Tollefson *et al.* [8]	2010 (n=1397)	12.7% (178/1378)	82.6%	5% (69/1378)	0.9% (13/1378) 54% (7/13) with FS(+)	FS(+) was associated with UUTR HR 4.88, 95% CI 3.02-7.90, p<0.001) Conversion of FS(+) to FS(-) was associated with low UUTR HR 4.39, 95% CI 2.59-7.43, p<0.001) No conversion of FS(+) was worse HR 7.37, 95% CI 4.3-16.4, p<0.01) p=0.04 UUTR was ipsilateral to the FS(+) in 64% (18/28)
Touma *et al.* [16]	2010 (n=301)	2.8% * (10/362) (*) ureter unit	-	2% (6/301) 67% with PS(-)	0%	FS(+) was not associated with UUTR and overall survival
Gakis *et al.* [9]	2010 (n=218)	6.9% (15/218) 4%* (17/425) (*) ureter unit	41.1%	2.3% (5/218) 10% PS(+) (1/10) 1.9% PS(-) (4/208) (p=0.03)	0.9% (2/218)	Conversion from FS(+) to PS(-) was associated with no UUTR
Kim *et al.* [19]	2015 (n=402)	5.2% (CIS and carcinoma only) 11.5% (46/402)	75.6%	2.7% (11/402)	0.2% (1/402)	FS(+) and PS(+) were not associated with UUTR
Reder *et al.* [20]	2015 (n=364)	6.3% *(48/768) CIS 3.8% *(29/768) carcinoma (*) ureter unit	-	2.7% None have FS(+)	-	FS(+) and PS(+) were not associated with CFS and OS
Moschini *et al.* [21]	2016 (n=1147)	25.4% (368)	48%	7.1% if FS(+) 4.5% if negative conversion 9.5% non negative conversion	-	FS(+) convertion to PS(-) was associated with low UUTR p<0.05 CFS p=0.01 OS p<0.05
Satkunasivam et al. [22]	2016 (n=2047)	8.6% (178/2047)	66.4%	1.4% (28/2047) 54% FS(-)	0% 14.2% of 21 NUT have incidental (CIS, pTa) at uretero-enteric anastomosis	FS(+) associated with UUTR HR 6.2, CI 2.9-13.5 PS(+) associated with UUTR HR 7.2, CI 2.7-18.9 p<0.001 FS(+) conversion to FS(-) was not associated with UUTR

Table 4.

Authors [Ref]	Year of publication Patients (n)	Pronostic factors for positive PS	Analysis	Type of study	Odds ratio OR (CI 95%)
Nakanishi *et al.* [27]	2006 n=158	CIS within bladder	Multivariate	Retrospective	3.33, CI : 1.05-10.53 (PS) p=0.04
Raj *et al.* [6]	2006 n=1330	CIS within bladder	Multivariate	Retrospective	3.99, CI : 1.87-8.51 p<0.0005 PS+: 30% (with bladder Cis) and 9% (without)
Osman *et al.* [7]	2006 n=100	FS(+) Male gender CIS within bladder	Univariate	Prospective	p<0.01 p=0.01 12.9% (no bladder Cis) versus 26.7% (bladder Cis) NS
Touma *et al.* [16]	2010 n=301	CIS within bladder CIS of prostatic urethra	Multivariate	Retrospective	p<0.02 p<0.02
Gakis *et al.* [9]	2011 n=218	FS(+) Tumor multifocality	Multivariate	Retrospective	p< 0.0001 p< 0.04
Gondo *et al.* [17]	2013 n=197	Tumor trigone location Clinical stage > or = cT3 Number of tumor (> or =3)	Multivariate	Retrospective	(*) for FS(+) and/or PS(+) *2.408, CI : 1.116–5.200 p=0.0252 *3.190, CI : 1.432–7.105 p=0.0045 *3.245, CI : 1.431–7.363 p=0.0048
Loeser *et al.* [24]	2014 n=243	CIS within bladder	Multivariate	Retrospective	0.85% (no bladder Cis) versus 35.6% (bladder Cis) p<0.0001
Zhou *et al.* [18]	2014 n=203	CIS within bladder	Multivariate	Retrospective	0% (no bladder Cis) versus 15.5% (bladder Cis) p<0.001
Kim *et a*l. [19]	2015 n=402	CIS within bladder Intramural invasion Lymp node status FS(+)	Multivariate	Retrospective	11.1, CI : 2.3-54.03 p=0.003 7.82, CI : 1.97-31.04 p=0.003 5.01, CI : 1.19-21.03 p=0.02 177.91, CI : 36.27-872.67 p<0.001
Moschini *et al.* [21]	2016 n=1447	CIS within bladder	Multivariate	Retrospective	3.83, CI : 1.83-8 (PS) p<0.001 6.40, CI : 2.86-14.3 (FS) p<0.001
Satkunasivam *et al.* [22]	2016 n=2047	Mucosal or ductal prostatic urothelial cancer	Multivariate	Retrospective	*1.78, CI : 1.11-2.86 (*) for FS(+)
Masson *et al.* [28]	2017 Cohorte A n=441 Cohorte B n=307	CIS within adder Hydronephrosis	Multivariate	Retrospective	Cohort A Hydronephrosis: Odds ratio [OR]=4.9, p=0.004 CIS: OR=3.9, p=0.01 Cohort B Hydronephrosis: [OR]=5.9, p=0.01 CIS: OR=3.4, p=0.10

Table 5.

References	Biases
3,6,8,10,11,15,19,21,22,23,24,25,36	Histological bias (mild atypia and dysplasia recorded at distal ureteral margin)
7,12,14,17,26,27,37	Bias due to low number of patients (< 200)
5,6,7,9,10,11,13,14,15,16,17,18,19,20, 22,24,25,26,27,28,37	Short-term follow-up (mean follow-up < 5 years)
7,8,9,10,12,13,15,17,18,19,20,25,26,28,36 4,5,6,11,14,22,24,31,33,34 3,4,5,6,14,21,22,24,27,31,32,33,34	Follow-up (imaging modalities) Not described IVP CTS
4,5,6,7,8,9,10,11,12,13,17,18,19,20,21,22,23,24,25,27, 28,31,32,34,36,37	Surgical technique: intraoperative management of ureteral length not described (made by the surgeon on a case by case basis)
3,4,5,6,7,8,9,10,11,12,13,15,16,17,18,19,20,21,22, 23,24,25,26,27,28,31,32,33,34,36	Multiplicity of surgeons
3,4,5,6,8,9,10,11,12,13,14,15,16,17,18,19, 20,21,22,23 24,25,26,27,28,31,32,33,34,36,37	Retrospective study (incomplete data, patients selection bias)
3,4,5,6,7,8,9,10,18,19,20,21,22,23,24,25,27,28,31,32,33,36,37	Additional treatment done before and/or after cystectomy (external beam radiation, chemotherapy) not specified