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Utility and significance of ureteric frozen section analysis during radical cystectomy

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Abstract

Objective—To assess the utility of routine frozen section analysis of ureters at the time of radical cystectomy (RC) for urothelial cancer (UC), and the long-term outcomes of adverse ureteric pathology.

Patients and Methods—Pathological data on 2 047 patients undergoing RC for UC with routine frozen section analysis of ureters (January 1971 to December 2009) were analysed. Univariate and multivariable logistic and Cox proportional hazards models were used to determine the risk of upper tract UC (UTUC) recurrence, local recurrence and overall survival in those identified as having adverse pathology (severe atypia/carcinoma *in situ* [CIS] or UC) at time of frozen section analysis.

Results—Adverse pathology was identified by frozen section analysis in 178 patients (8.6%). Frozen section analysis was found to have poor sensitivity in identifying adverse pathology (59.1%), which was improved in patients with preoperative CIS (68.0%). After a median (interquartile range) follow-up of 12.4 (1.9–10.1) years, 28 patients (1.4%) developed UTUC recurrence. There were no uretero-enteric anastomotic recurrences. Adverse pathology on frozen section analysis was associated with UTUC recurrence on univariate analysis (hazard ratio [HR] 6.2, 95% confidence interval [CI] 2.9–13.5), but 15/28 patients (54%) with UTUC recurrence had benign ureteric frozen section analysis on initial sectioning. Adverse pathology on frozen section analysis was not independently associated with the risk of local recurrence (HR 1.08, 95% CI 0.61–1.89) or overall survival (HR 1.12, 95% CI 0.94–1.35) in multivariate models.

Conclusions—Ureteric frozen section analysis has poor sensitivity and may be marginally improved in pre-existing CIS. UTUC recurrence is rare and can occur despite negative frozen section analysis. Our data question the utility of routine frozen section analysis of the distal ureteric margin at the time of RC.

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Conflict of Interest

None declared.

Keywords

urothelial carcinoma; radical cystectomy; frozen section analysis; ureter; upper tract urothelial carcinoma

Introduction

Radical cystectomy (RC) remains the standard of care in the treatment of muscle-invasive urothelial cancer (UC). A panurothelial field defect suggests that, even after RC, the residual urothelium is at risk of upper tract UC (UTUC), including recurrence at the uretero-enteric anastomosis [1]. The incidence of UTUC after RC ranges from 0.75 to 6.4% [2], but is lower at the uretero-enteric anastomosis (0.2–1%) [3–7].

Ureteric frozen section analysis at the time of RC for UC was introduced to identify and excise all potentially malignant tissue and reduce the risk of local recurrence [8]. The utility of this approach to accurately identify abnormal ureteric pathology intra-operatively and whether there is any benefit to aggressively resecting carcinoma *in situ* (CIS) at the ureteric margin has been questioned [3,9–11]. The practice of contemporary frozen section analysis remains controversial. Some advocate that frozen section analysis should be selectively used given the low rate of UTUC, poor association with UTUC, lack of impact on overall survival [4,5,12–14] and uncertainty in reliably converting a positive frozen section analysis to a negative one [7]. The existence of 'skip lesions' (abnormalities occurring proximal to a benign frozen section analysis) is a further argument against routine frozen section analysis [15]. Others argue that the association between an abnormal frozen section analysis and UTUC allows closer, risk-adapted surveillance, and that frozen section analysis can guide sequential intra-operative resection to achieve benign margins and decrease recurrence [6,15,16].

The practice of frozen section analysis of distal ureters at the time of RC has remained constant at the University of Southern California since the early 1970s [17]. In the present study, we sought to address the operating characteristics of frozen section analysis as a diagnostic test, and ultimately the association between adverse frozen section analysis pathology and the risk of UTUC, local recurrence and overall survival.

Patients and Methods

Study Cohort

Consenting patients that underwent open RC and extended pelvic lymph node dissection for primary UC of the urinary bladder at the University of Southern California are prospectively followed in an institutional review board-approved database. This database is maintained by a single dedicated database manager (G.M.) with follow-up and reliable capture of recurrences by direct communication with primary care providers and referring physicians. Reliable capture of mortality is confirmed using the Social Security Death Index. We identified 2 572 patients from January 1971 to December 2009 for inclusion in the database. We excluded patients with concomitant UTUC or those with suspicion for UTUC on preoperative imaging, as well as patients undergoing RC without intent to cure. The study

cohort consisted of 2 047 patients treated for UC of the bladder in whom pathological information from intra-operative frozen section analysis of ureters was available.

Surgical and Pathological Technique

All patients underwent open RC with extended pelvic lymph node dissection and urinary diversion as previously described [18]. Ureteric margins are sent for frozen section analysis at the time each ureter is clipped and divided as standardized practice. Subsequent ureteric resections are made at the discretion of the individual surgeon based on frozen section analysis results, but in general, if there is a positive ureteric margin, sequential resections are performed until a negative margin is obtained. At the time of ureteric anastomosis, the margin of ureter is trimmed, embedded in paraffin and step-sectioned for permanent pathological analysis. This represents the final proximal ureteric margin. Dedicated genito-urinary pathologists at USC during the majority of the study period performed all pathological analyses (frozen section analysis and permanent).

Patient Follow-up

Patients are generally followed with clinical examination and routine blood tests every 4 months in the first year, every 6 months in the second year and annually thereafter. Radiological evaluation consists of chest X-ray and either intravenous pyelogram (until the mid-1990s) or abdominal and pelvic imaging (ultrasonography or CT, based on clinical indication) performed at 4 months postoperatively, and every 6 months thereafter, for at least a period of 3 years. Surveillance protocols are not modified based on abnormal ureteric margin status.

Outcome Measures and Statistical Analysis

The primary outcome measure was UTUC recurrence (including anastomotic recurrence). Secondary outcomes were local recurrence (defined as relapse of disease in the pelvic or urethral regions) and overall survival. For the purposes of our analysis, we grouped together mild and moderate atypia, referred to in the present study as ‘atypia’. Severe atypia was grouped with CIS, referred to in the present study as ‘CIS’. Abnormal pathology was defined as anything other than benign tissue, while CIS and UC are grouped as ‘adverse’ pathology. We compared the pathological results of frozen section analysis with final ureteric permanent section to assess sensitivity and specificity. We analysed the intra-operative sectioning strategy of patients with electronic records, in whom pathology reports were available for re-review. Specifically, those with an abnormal frozen section analysis, as well as patients who presented with eventual UTUC recurrence were reviewed. Multivariable logistic regression was performed to determine the predictors of adverse ureteric margin pathology. Univariate models were used to assess predictors of UTUC recurrence because events rates were insufficient (28 events) for multivariable analysis. Multivariable Cox proportional hazards regression analysis was used to assess the predictors of local recurrence and overall survival. Data were analysed using SAS 9.1.3 (SAS Institute, Cary, NC, USA). A two-sided P value of <0.05 was considered to indicate statistical significance.

Results

A total of 2 047 patients underwent RC for UC of the bladder with intra-operative frozen section analysis of ureters between 1971 and 2009. The median (interquartile range [IQR]) follow-up was 12.4 (1.9–10.1) years. The demographic characteristics of the study cohort are shown in Table 1. Ureteric frozen section analysis identified normal urothelium (1 588 patients, 77.6%), mild atypia (194 patients, 9.5%), moderate atypia (87 patients, 4.3%), severe atypia or CIS (78 patients, 3.8%), and urothelial carcinoma (100 patients, 4.9%). The incidence of abnormal or adverse pathology at the time of frozen section analysis was 22.4% (460/2 047 patients) and 8.6% (178/2 047 patients), respectively. Mucosal or ductal prostatic urothelial cancer (UC; odds ratio 1.78, 95% CI 1.11–2.86), but not stromal invasion, was associated with adverse ureteric margin pathology on frozen section analysis in males after adjusting for age, pathological grade and stage, preoperative CIS, lymphovascular invasion and diversion type (data not shown).

Of 178 patients, 95 (53%; or 115 ureters) with adverse pathology were available for detailed medical record review using electronic records to assess the intra-operative ureteric frozen section analysis strategy. A total of 103 (89.6%) ureters underwent ≥2 frozen section analyses after the initial frozen section analysis, resulting in successful intra-operative conversion to benign histology in 77 ureters (66.4%). Final (permanent) histology revealed adverse pathology of the proximal-most section in 3.2% of cases (66/2 047 patients), of which 59.1% had adverse frozen section analysis of the distal ureter. Compared with final, permanent section pathology as the ‘gold standard’, intra-operative frozen section analysis was found to have poorer sensitivity for the detection of CIS and UC (Table 2). In the subset of patients with preoperatively identified CIS in the bladder, the sensitivity of frozen section analysis for the detection of UC and adverse pathology was improved from 43.3 to 72.7% and from 59.1 to 68.0%, respectively.

The median (IQR) follow-up of patients with abnormal ureteric pathology and adverse ureteric pathology was 6.1 (1.7–15.6) years and 5.0 (1.3–9.9) years, respectively. Twenty-eight (1.4%) patients developed upper tract recurrence at a median (IQR) interval from RC of 2.3 (1.1–4.4) years. Recurrences were primarily in the renal pelvi-calyceal urothelium (25 patients), with two patients presenting with concomitant renal and ureteric recurrence, while a single patient had isolated ureteric recurrence. No anastomotic recurrences were identified. The majority of these patients had organ-confined bladder UC (22/28 patients, 79%). A significant number of patients with UTUC recurrence had benign ureteric frozen section analysis on initial sectioning (15/28 patients, 54%) while adverse pathology was identified in 10/28 patients (36%; Table 3). Ten ureters with abnormal pathology had serial sectioning (up to four frozen sections in one situation), to establish a benign frozen section successfully in nine. Despite achieving intra-operative benign margins with sequential sectioning, three of the nine had abnormal adverse proximal ureteric margins on final histology. There was 100% concordance with the side of UTUC recurrence and the side of initial adverse pathology, despite the successful conversion to benign intra-operative margins in 90% of cases (and benign permanent sections of the proximal ureter).

Of the 28 patients with upper tract recurrence, 27 were treated by a nephro-ureterectomy, while one patient was treated with ureteric resection and creation of an ileal ureter. Of the available nephro-ureterectomy pathology for review, three of 21 (14.2%) specimens were found to have incidental adverse pathology (CIS or pTa) at the uretero-enteric anastomosis. Two of these three patients had CIS at the final proximal ureteric margin.

Adverse pathology on frozen section analysis was associated with an increased risk of UTUC on univariate analysis (hazard ratio [HR] 6.2, 95% CI 2.9–13.5). Specifically, both CIS (HR 5.68, 95% CI 1.87–17.3) and UC (HR 7.69, 95% CI 2.96–20.01) identified at frozen section analysis were associated with increased risk. Adverse pathology on permanent section of proximal ureters was associated with UTUC recurrence on univariate analysis (HR 7.2, 95% CI 2.7–18.9; $P < 0.001$). Despite the successful conversion of an adverse frozen section analysis to an intra-operative benign ureteric margin, the increased risk of UTUC persisted on univariable analysis, although the effect was no longer significant (OR 1.97, 95% CI 0.21–18.3). Prostatic UC involving the stroma (HR 3.3, 95% CI 1.09–9.97; $P = 0.034$), but not prostatic ducts (HR 2.54, 95% CI 0.74–8.78; $P = 0.14$) was associated with UTUC recurrence on univariate analysis.

Adverse pathology on frozen section analysis was not significantly associated with the risk of local recurrence (HR 1.08, 95% CI 0.61–1.89), which occurred in 133 patients (Table 4). At the time of most recent follow-up, 1 279 patients had died. The median survival of those with adverse frozen section analysis pathology was 5.6 years. Adverse frozen section analysis was not independently associated with overall survival (HR 1.12, 95% CI 0.94–1.35; Table 5).

Discussion

To our knowledge, the present study represents the largest systematic use of ureteric frozen section analyses during RC and the longest follow-up of adverse ureteric margin pathology reported in the literature. Our data show an overall low likelihood of UTUC recurrence (1.4%), which is consistent with previously reported rates [2]. Adverse pathology identified at the time of frozen section analysis was associated with increased risk of UTUC, yet approximately half of UTUC occurred in the context of benign ureteric frozen section analysis. Importantly, given the retrospective nature of our cohort, we cannot exclude the possibility that the absence of anastomotic recurrences was attributable to our strategy of repeated sectioning to achieve benign intra-operative margins in those with adverse pathology. Furthermore, the finding of UC in ~5% of frozen section analysis (with a sensitivity of 43%) underscores the benefit of frozen section analysis, and the clinical risk associated with discontinuing this procedure altogether.

The false-negative rate of frozen section analysis in our series (41% for adverse pathology) is relatively high and consistent with the pagetoid spread of CIS [13]. While the authors of a study with a 1% false-negative rate [16] have suggested restricting frozen section analysis to those with bladder CIS, this strategy did not substantially decrease the false-negative rate (32%) in the present study. Arguably, the false-negative rate and the ability to confidently exclude a diseased ureter is the most important characteristic of frozen section analysis as a

diagnostic test. Despite the operating characteristics of frozen section analysis, there is undoubtedly a relationship between UTUC and adverse frozen section analysis that is a positive association [2,4]; however, the strength of this association is unknown because we cannot adjust for other confounders of this relationship owing to the low number of UTUC events and also because of the competing risk of the bladder primary (patients that may be destined for UTUC recurrence may never survive long enough to experience it). Frozen section analysis probably has limited benefit in guiding surveillance of patients and influence oncological outcomes over other established risk factors [13]. This is consistent with the absence of an association between adverse frozen section analysis and local recurrence, as well as overall survival. Furthermore, it should be emphasized that, while frozen section analysis may give insight into the extent of urothelial abnormalities (e.g. multiple abnormal margins), its primary use is for intra-operative decision-making. By contrast, adverse proximal permanent margins, which were associated with UTUC recurrence, can be used to guide risk-adapted surveillance.

The process of sequentially sectioning the ureter to achieve a negative margin may have decreased uretero-enteric anastomotic recurrences, but it does not preclude the possibility of upper tract recurrence, consistent with the panurothelial nature of UC. Other studies have reported an inconsistent relationship between a positive frozen section analysis and UTUC [3,7,9]. Tollefson et al. [6], however, showed that patients with initial positive margins converted to negative margins had a lower risk of recurrence than those with an initial positive margin that could not be converted to negative. It is unclear whether this effect would have only been observed in those patients with anastomotic recurrences, which occurred more frequently in this study (13/69 patients) and may also reflect the extent of pan-urothelial disease in the two groups and not specifically margin status.

Despite its strengths in terms of follow-up length and cohort size, the present study is limited by retrospective data collection at a single institution. Our database did not capture the final, permanent section interpretation of the same residual tissue from the frozen section of the distal ureteric margin, as it is not standard practice at our institution. As such, we were not able to delineate skip lesions, ureters in which the final, proximal permanent margin is abnormal, despite a benign distal margin [15], from differences owing to the operating characteristics of frozen section analysis because the same tissue was not processed by permanent section. As UTUC recurrence is relative low, an adequately powered randomized controlled trial remains a challenge, and thus, the present study using our established database with robust follow-up, together with standardization of surgery, ureteric frozen section analysis and permanent pathology in all patients, provides important insights.

In conclusion, the present data call into question the utility of routine frozen section analysis of the distal ureteric margin at the time of RC. Routine frozen section analysis of the distal ureteric margin has poor sensitivity, which is marginally improved in patients with pre-existing CIS. The predictive utility for upper tract recurrence is questionable and permanent ureteric margins of the proximal resection may be sufficient to predict potential upper tract recurrence and guide risk-adapted surveillance. The process of sequential sectioning may remain valuable in preventing anastomotic recurrence and requires prospective evaluation.

Abbreviations:

RC	radical cystectomy
UC	urothelial cancer
UTUC	upper tract urothelial cancer
CIS	carcinoma *in situ*
HR	hazard ratio
IQR	interquartile range

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Table 1

Demographic, pathological and clinical characteristics of the study cohort ($N = 2\ 047$).

Characteristic	*n* (%)
Age	
<60 years	540 (26.4)
60–69 years	693 (33.9)
70–79 years	635 (31.0)
≥80 years	179 (8.7)
Gender	
Male	1 621 (79.2)
Female	426 (20.8)
Pathological stage	
pT0	152 (7.4)
pTa/pTis	326 (15.9)
pT1	358 (17.5)
pT2A	205 (10.0)
pT2B	256 (12.5)
pT3A	189 (9.2)
pT3B	352 (17.2)
pT4A	190 (9.3)
pT4B	19 (0.9)
Pathological grade	
Low	330 (16.1)
High	1 717 (83.9)
CIS	
Absent	1 480 (72.3)
Present	567 (27.7)
Prostatic pathology	
None	1 345 (65.7)
Urethral or Ductal UC	113 (5.5)
Stromal UC	163 (8.0)
Female	426 (20.8)
Urethrectomy	145 (0.07)
Diversion type	
Ileal conduit	418 (20.4)
Neobladder	1 245 (61.3)
Continent catheterizable stoma	375 (18.3)
Chemotherapy	
Neoadjuvant	132 (6.5)
Adjuvant	427 (20.9)
Preoperative radiation	140 (6.8)

CIS, carcinoma in situ.

Table 2

Sensitivity and specificity of intra-operative frozen section analysis calculated in relation to the final permanent section of the proximal margin (gold standard).

Frozen section	Permanent section	
	Abnormal	**Normal**
Abnormal, *n*	258	202
Normal, *n*	77	1 510
Sensitivity, %	77.0	
Specificity, %	88.2	
	Atypia	**No Atypia**
Atypia, *n*	204	155
No atypia, *n*	101	1 587
Sensitivity, %	66.9	
Specificity, %	91.1	
	CIS	**No CIS**
CIS, *n*	12	69
No CIS, *n*	24	1 942
Sensitivity, %	33.3	
Specificity, %	96.6	
	UC	**No UC**
UC, *n*	13	85
No UC, *n*	17	1 932
Sensitivity, %	43.3	
Specificity, %	95.8	
	Adverse pathology	**No adverse pathology**
Adverse pathology, *n*	39	139
No adverse pathology, *n*	27	1 842
Sensitivity, %	59.1	
Specificity, %	93.0	
Subset of patients with preoperative bladder CIS		
	UC	**No UC**
UC, *n*	8	38
No UC, *n*	3	518
Sensitivity, %	72.7	
Specificity, %	93.2	
Subset of patients with preoperative bladder CIS		
	Adverse pathology	**No adverse pathology**
Adverse pathology	17	52
No adverse pathology, *n*	8	490
Sensitivity, %	68.0	
Specificity, %	90.4	

CIS, carcinoma in situ; UC, urothelial cancer.

Table 3

Ureteric margin pathology, intra-operative resection strategy and outcomes in 28 patients (55 ureters total as one patient had a solitary kidney) with upper tract recurrence.

	Left frozen section analysis (27), *n*	**≥1 subsequent resection(s), *n***	**Successful conversion to benign margin. *n***	**Ipsilateral upper tract recurrence. *n* (%)**
Benign	20	0	n/a	8 (42)
Atypia	2	0	n/a	1 (50)
CIS	5	5	4	5 (100)
UC	0	0	0	0
	Right frozen section analysis (28)			
Benign	20	0	n/a	7 (35)
Atypia	3	1	1	2 (67)
CIS	3	2	2	3 (100)
UC	2	2	2	2 (100)

CIS, carcinoma in situ; UC, urothelial cancer.

Table 4

Adjusted probability of local recurrence after radical cystectomy from multivariable Cox regression analysis.

Variable	HR	95% CI	*p*
Age	1.01	1.00–1.03	0.80
Gender			
Male	1.00		
Female	0.68	0.42–1.11	0.12
Pathological stage			
Organ-confined	1.0		
EV	2.46	1.56–3.87	0.0001
Pathological grade			
Low grade	1.0		
High grade	2.02	1.03–3.94	0.04
Multifocality	1.22	0.85–1.75	0.28
Lymphovascular invasion	1.04	0.69–1.56	0.85
Node-positive	3.66	2.18–6.15	<0.0001
Chemotherapy			
None	1.00		
Neoadjuvant	1.63	0.86–3.10	0.13
Adjuvant	0.64	0.40–1.03	0.07
Positive soft tissue margin	2.29	0.68–7.69	0.18
Adverse ureteric pathology on frozen section analysis	1.08	0.61–1.89	0.80

EV, extra-vesicle; HR, hazard ratio. HRs are adjusted for each of the listed variables mutually. Local recurrence is defined as urethral or pelvic recurrence of urothelial cancer.

Table 5

Adjusted probability of overall survival after radical cystectomy from multivariable cox regression analysis.

Variable	HR	95% CI	*p*
Age	1.04	1.04–1.05	<0.001
Gender			
Male	1.00		
Female	1.04	0.91–1.19	0.58
Pathological stage			
Organ-confined	1.0		
EV	1.86	1.60–2.17	<0.001
Pathological grade			
Low grade	1.0		
High grade	1.31	1.09–1.57	0.004
Multifocality	0.96	0.86–1.09	0.55
Lymphovascular invasion	1.25	1.10–1.43	0.001
Node-positive	3.09	2.62–3.65	<0.001
Chemotherapy			
None	1.00		
Neoadjuvant	1.50	1.20–1.89	<0.001
Adjuvant	0.61	0.52–0.72	<0.001
Positive soft tissue margin	1.74	1.05–2.89	0.03
Adverse ureteric pathology on frozen section analysis	1.12	0.94–1.35	0.21

EV, extra-vesicle; HR, hazard ratio. HRs are adjusted for each of the listed variables mutually.