

Utility of Routine Intraoperative Ureteral Frozen Section Analysis at Radical Cystectomy: Outcomes from a Regional Australian Center

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Key Words

Frozen section • Ureter • Cystectomy • Mortality • Cost effectiveness

Abstract

Introduction: The objective of this study was to look at the usefulness and cost effectiveness of intraoperative frozen section analysis (FSA) of the ureters at the time of radical cystectomy. **Methods:** Pathology notes of patients undergoing radical cystectomy for primary bladder cancer between the years 2000–2015 at our institution were reviewed. **Results:** A total of 196 ureteric specimens from 98 patients were reviewed. Of the 98 patients, 9% (n = 9) had positive ureteric margins, of which all were $\geq T2$, with 44% (4 of 9) being T = 4. In all cases of positive FSA, preoperative clinical staging was $\geq T2$. In cases where cancer staging was upgraded post-cystectomy, there were no cases of positive FSA. After adjusting for tumor stage in $\geq T2a$, using Cox regression analysis, positive frozen section was associated with a 4.2 fold increase in overall mortality (95%CI 1.3–13.8; p = 0.02). Cost associated with FSA was AU\$1,351.90 to obtain 1 positive result. **Conclusion:** Patients with positive ureteric FSA are at higher risk of mortality post cystectomy, despite excision to negative tissue. However, FSA of the distal ureters at cystectomy were unlikely to be positive unless the bladder cancer stage was $\geq T2$. Hence, routine ureteric FSA may not be necessary in patients undergoing cystectomy for non-muscle invasive bladder tumors.

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Introduction

Bladder cancer is a commonly occurring cancer within the Australian population, being the fourth most common solid organ tumor in men, and seventh in women [1]. Radical cystectomy is the treatment of choice in high-risk bladder cancer.

The European Association of Urology guidelines in 2011 recommended the use of intraoperative frozen section analysis (FSA) of ureters during radical cystectomy [2]. However, the influence of intraoperative FSA during radical cystectomy on intraoperative management, prognosis and cost remains a topic of much debate. It adds both a physical burden to the patient, with longer operating time and anesthesia time, as well as economic burden to the health system. Some studies suggest no overall clinical difference in outcome [3]. As such, the current EAU guidelines do not include the use of intraoperative FSA [4]. However, many regional centers in Australia continue to routinely send distal ureters for FSA at the time of cystectomy mainly owing to prognosis and long-term follow-up of regional patients, where some patients have limited access to healthcare. To our knowledge, there are no studies investigating this routine practice and its cost effectiveness in regional Australian centers.

As such, we aimed to investigate the usefulness and cost effectiveness of intraoperative FSA of the ureters at the time of radical cystectomy at a regional hospital in Australia.

Table 1. Histological characteristics of radical cystectomy specimens

	Frequency	Percent (%)
Pathological stage		
T0, Tx	12	12
CIS	6	6
Ta	1	1
T1	7	7
T2	34	33
T3	24	24
T4	14	14
Soft tissue margin		
Positive	27	28
Negative	71	72
Ureteric margin		
Positive	9	9
Negative	89	91
Urethral margin		
Positive	19	19
Negative	63	64
Not reported	16	16
Lymphovascular invasion		
Positive	44	45
Negative	54	55

Table 2. Frozen section positivity according to pathological staging

Stage	Number (%)	FS positive (%)
T0, Tx	12 (12)	0 (0)
CIS	6 (6)	0 (0)
Ta	1 (1)	0 (0)
T1	7 (7)	0 (0)
T2	34 (33)	3 (9)
T3	24 (24)	1 (4)
T4	14 (14)	5 (36)

Methods

A retrospective notes review of all patients undergoing a radical cystectomy at our institution from January 2000 to August 2015 was conducted. All patients who underwent cystectomy for primary bladder cancer (including transitional cell carcinoma and squamous cell carcinoma) were included. It was routine practice to send frozen sections of the distal ureters in all patients at the time of cystectomy. Therefore all patients had FSA.

Patients were excluded if they had a cystectomy performed for non-primary bladder cancer reasons (i.e. rectal cancer invasion, chronic cystitis, lymphoma invasion). Data gathered included gender, age, preoperative biopsy stage, postoperative pathological stage, tumor grade, nodes, ureteric margins, soft tissue margins, urethral margins, length of follow-up and cancer type. Positive margins were defined as the presence of urothelial carcinoma, carcinoma *in situ* (CIS) or high-grade dysplasia within the initial frozen section specimen. If positive margins were identified more ureter would be resected until the margins were negative. Staging was based on the 2010 TNM staging system.

Table 3. Preoperative pathological staging, with subsequent up- and down-staging

Preoperative staging	Frequency (%)	Up-staged (%)	Down-staged (%)
CIS	12 (12)	4 (33)	1 (8)
Ta	1 (1)	0 (0)	0 (0)
T1	13 (13)	5 (38)	3 (23)
T2	51 (52)	16 (31)	9 (18)
T3	15 (15)	0 (0)	5 (33)
T4	5 (5)	0 (0)	1 (20)

Chi-squared analysis was performed to compare FSA positivity of distal ureters with gender, age, stage, tumor, grade, nodal status, concomitant CIS and ureteric involvement. A cox-proportional hazard analysis for risk factors was performed. Finally, a cost-analysis was also performed based on 2015 fees. SPSS statistical software (version 17.0) was used for statistical analysis.

Results

Over the years 2000–2015, a total of 116 patients underwent cystectomy at our center of which 102 patients had a cystectomy for primary bladder cancer. Four of the patients had missing data and were excluded from the analysis, resulting in 98 patients in the final analysis. The total number of urologists involved were 6, with 2 primary pathologists reporting the results. Male to female patient ratio was 67:31 (2:1). Mean length of follow-up was 70 months. Four patients had neoadjuvant chemotherapy in our regional center for the duration of the study. The adjuvant chemotherapy data was not available.

Histology of the specimens showed 92 urothelial carcinomas, 5 small cell carcinomas, and 1 neuroendocrine tumor. Histological features of the specimens including distribution of tumor stages are summarised in table 1. All patients undergoing radical cystectomy had ureters sent for frozen section, of which 9% (n = 9) samples were positive on frozen section. In all cases of positive frozen section ureteric margins, pathological staging was \geq T2, with the greatest frequency of positive margins seen in T4 (n = 5), as shown in table 2. Of the 9 patients with positive frozen sections, 3 had CIS at the margin and the rest urothelial carcinoma.

Preoperative biopsy was also considered as a possible predictor of ureteral FSA positivity. One patient had preoperative clinical data missing. Distribution of preoperative staging, and subsequent upstaging and downstaging post-cystectomy is in table 3. Of the 97 patients, 27 had a preoperative stage of $<$ T2; of whom 0 subsequently had a positive ureteric margin on FSA. Of remainder 71

Table 4. Preoperative staging with ureteric margin positivity

Preoperative staging	Number*	Positive ureteric margin on FSA
T0/CIS/Ta/T1	26	0 (0)
≥ T2	71	9 (13)
T0/CIS/Ta/T1	9	0 (0)
Upgraded to ≥ T2		

* One preoperative clinical data missing.

Table 5. Overall survival: multivariate analysis using cox regression analysis

Variable	Hazard ratio	95%CI	p
T stage: > T2	4.6	1.9–11.4	0.001
Nodal positivity: ≥ 1	1.5	0.9–2.7	0.142
Metastases: ≥ 1	0.4	0.5–1.5	0.353
Positive ureteric margin	4.2	1.3–13.8	0.016
Positive soft tissue margin	0.7	0.3–2.0	0.54

patients who had a preoperative stage of ≥ T2, 9 subsequently had a positive ureteric margin on FSA. Of the 9 cases of < T2 that eventually upgraded to ≥ T2, 0 had a positive ureteric FSA (table 4).

Of the 9 patients with concomitant or primary CIS, none had positive ureteric margin on FSA. After adjusting for tumor stage in ≥ T2a, nodal positivity, metastases and positive soft tissue margins using Cox regression analysis, positive frozen section was associated with a 4.2 fold increase in overall mortality (95%CI 1.3–13.8; $p = 0.016$) (table 5). Ureteric FS positivity was not involved in positive lymph nodes ($p > 0.05$).

Cost analysis was performed on ureteric FSA. Based on 2015 Medicare fees, FSA of both ureters cost AU\$ 245.80. The total amount spent on FSA for CIS/T1 bladder tumors was AU\$ 6,390.80. Total amount spent on FSA for ≥ T2 bladder tumors was AU\$ 17,697.60. It requires 9 FSAs to detect 1 positive result, costing AU\$ 2,236.80 to detect 1 positive result. If limited to ≥ T2 bladder tumors, it requires only 7 frozen sections to detect 1 positive result, and the cost decreases to AU\$ 1,351.90 to detect 1 positive result.

Discussion

Current practice guidelines recommend the use of radical cystectomy with pelvic lymph node dissection

as the treatment option for non-metastatic, muscle invasive bladder cancer. EAU guidelines also recommend the use of FSA of the ureters at the time of surgery [2, 5]. However, the use of ureteric FSA at the time of surgery remains a point of much debate [6–9].

Our results find that while positive ureteric margins is associated with poorer overall survival; incidence of positive margins was fairly low (9%, $n = 9$), with the incidence of positive ureteric margins being 0 in patients with a preoperative pathological stage of $T < 2$, even if they were up-staged postoperatively. Even in cases with concurrent CIS, ureteric margins remained negative in all cases. These results would suggest the selective use of ureteric FSA in patients with a preoperative pathological staging of ≥ T2a only.

Our findings are consistent with several other studies conducted across the world. Several studies place the incidence of positive ureteric margins on FSA at 4–15% [10–12]. Similarly, ureteric margin positivity has not been shown to be associated with lymph node positivity [13]. Sensitivity of intraoperative FSA has been shown to be quite variable 45–80%; while specificity has always remained high at 95–99% [10].

Other studies have also shown that while positive ureteric margins on FSA has been associated with upper urinary tract recurrence, it has not been associated with poorer disease-specific survival rates [7, 13, 14]. This is in contrast to our results that support the use of ureteric positivity as a predictor of poorer overall survival rates. However, it should be kept in mind that our study did not look at upper urinary tract recurrence and disease-specific survival.

It's also been suggested that upper urinary tract recurrence may be more prone to occur in patients with cancer involvement at the intramural or juxtavesical ureter [15, 16], or in patients with CIS of the bladder [3, 17]; with ureteric positivity being an associated but non-independent risk factor for recurrence.

Practical concerns to consider include the risk of uretero-enteric anastomotic recurrence in patients with positive ureteric margins. Several studies have observed rates of anastomotic recurrence of about 0–1%, despite the presence of CIS or urothelial cancer in 14% of nephron-ureterectomy specimens [3, 15]. While these rates are low, the effect of frozen section guided resection cannot be determined. However, it should also be considered that even in the presence of negative margins, uretero-enteric recurrence can still occur.

Our cost analysis places the cost of obtaining one positive result at AU\$ 2,236. Few studies have looked at the

cost associated with ureteric FSA. Our result was only marginally higher than Touma et al. [18], which reported a cost of CAN\$ 2,080 (equivalent to AU\$ 2,100). However, we found that diagnostic yield can potentially be increased by limiting the use of ureteric FSA to patients who are at high risk of ureteral abnormalities, such as in the presence of bladder CIS or in patients with a preoperative staging of \geq T2a.

Results of this study may be limited by its retrospective nature. Surgical guidelines and practices have improved and changed significantly over the past 15 years. Surgical practices are also likely to vary between surgeons, possibly affecting margin positivity [19]. In addition, this study had a relatively small number of patients, with even fewer numbers having concurrent or primary CIS.

Conclusion

Patients with positive ureteric FSA are at higher risk of overall mortality post-cystectomy, despite excising the ureter until a negative segment is achieved. FSA of the distal ureters at cystectomy are however unlikely to be positive unless the bladder cancer stage is \geq T2. Omitting routine ureteric FSA in patients undergoing cystectomy for non-muscle invasive bladder tumors may therefore provide an economic benefit without impacting on clinical outcome.

Ethics Approval

Ethics approval was obtained from the institutional ethics committee. Ethical approval in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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