

## Lessons Learned from Routine Intraoperative Ureteral Margin Frozen Sections during Radical Cystectomy

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### Abstract

**Introduction:** We examined the practice patterns of intraoperative ureteral frozen section during radical cystectomy and the impact of ureteral margin positivity on operative characteristics and oncologic outcomes.

**Methods:** The records of patients who underwent radical cystectomy at our institution from 2004 to 2011 were identified. Intraoperative ureteral frozen section characteristics were examined, including number, laterality, positivity, conversion to negative and final permanent section status. Logistic regression analysis was performed for predictors of operative time, change in urinary diversion, and biopsy confirmed upper tract recurrence and metastasis.

**Results:** A total of 590 intraoperative ureteral frozen sections were sent for analysis from 241 patients (mean age 69 years). The sections were positive in 12.9% of cases and conversion to negative was accomplished in 82%. Multiple sections were associated with longer operating time (561 vs 511 minutes,  $p=0.011$ ). Sensitivity for the sections was 100% and specificity was 93.6%. Taking multiple ureteral resections did not alter the planned urinary diversion in any patient or increase perioperative complication rates. At a mean followup of  $22\pm 19.8$  months, 7 patients (3%) experienced upper tract recurrence. Intraoperative ureteral frozen section conversion to negative was associated with improved overall survival but not with upper tract recurrence.

**Conclusions:** Our practice of taking intraoperative ureteral frozen sections provided excellent sensitivity and specificity, and the prolonged operative time did not translate into increased perioperative complications. Conversion of positive to negative was associated with improved overall survival, independent of patient comorbidities and post-operative complications. No association was seen with upper tract recurrence but this was likely due to our high conversion rate to negative margins (82%), negative permanent section ureteral margin status in 97% of cases and the long followup time needed to demonstrate an association.

*Key Words:* urinary bladder neoplasms, ureteral neoplasms, cystectomy, frozen section, biopsy

### Abbreviations and Acronyms

CIS = carcinoma in situ  
DSS = disease specific survival  
IUFS = intraoperative ureteral frozen section  
OS = overall survival  
UTR = upper tract recurrence

The gold standard treatment with curative intent for muscle invasive bladder cancer is radical cystectomy with pelvic lymphadenectomy. The objective is complete surgical extirpation of tumor, lymph nodes and associated pelvic organs

with achievement of negative surgical margins.<sup>1,2</sup> Patients being treated for bladder urothelial cell carcinoma are at an increased risk for upper tract urothelial carcinoma compared to the general population.<sup>3,4</sup> The presence of carcinoma in situ in the bladder, multifocal disease, and ureteral and urethral involvement have been shown to increase this risk.<sup>4,5</sup>

Positive margins have been associated with disease recurrence for most urological cancers including prostate, kidney and bladder.<sup>6-8</sup> However, the influence of ureteral margin status on bladder cancer recurrence is less clear. Some studies have suggested that an involved ureter in an enteric diversion increases the risk of anastomotic and/or upper tract recurrence.<sup>9</sup>

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Thus, intraoperative ureteral frozen sections and the need for sequential excision of diseased distal ureteral segments to achieve a negative margin have been proposed.

Prior studies examining the influence of ureteral margin status have yielded conflicting results. Although older studies initially supported the routine practice of IUFS, more recent studies suggest that the practice be reserved for patients with high risk multifocal disease, citing low impact on survival outcomes and high costs.<sup>10</sup> We sought to determine the impact of IUFS and final margin status on UTR, disease specific survival and overall survival. We also assessed the impact of serial resectioning on intraoperative findings, planned vs actual diversion type and postoperative complications. Finally, we compared IUFS with permanent sections to assess sensitivity and specificity of this practice. This study addresses several controversial points regarding routine IUFS by reporting our modern experience in a consecutive patient series.

## Materials and Methods

### *Inclusion Criteria and Data Collection*

The institutional review board approved Urologic Oncology Database was queried for all patients undergoing radical cystectomy for urothelial cell carcinoma and creation of urinary diversion at our institution between 2004 and 2011. Inclusion criteria consisted of pathological stage T1-4, N0-2, M0 urothelial cell carcinoma. Operative reports and pathology reports were carefully examined for practice patterns of IUFS, including the number of sections per ureter per patient, laterality, positivity, histology, conversion to negative and length of ureteral resection. Finally, ureteral permanent section pathology and final margin status for each patient were examined and compared to IUFS.

### *IUFS*

Operative methods were consistent among surgeons. Briefly, 1 to 2 cm sections of both ureters at the distal transected end were excised and sent for frozen section pathology. A positive result was defined as urothelial cell carcinoma, CIS or severe dysplasia/atypia suspicious for carcinoma, resulting in subsequent resection from the distal end until a negative result was obtained. Serial resectioning that did not produce a negative result was abandoned at the discretion of the surgeon.

### *Statistical Analysis*

The Cox proportional hazards method was used to identify predictors of positive IUFS and conversion to negative, including age, race, comorbidities, year of surgery, clinical stage, pathological features on transurethral resection (grade, CIS, lymphovascular invasion), clinical lymph node status, prior intravesical therapy and neoadjuvant chemotherapy (table 1). Operative outcomes such as diversion type, estimated blood loss, blood transfusion, operative time, and postoperative

**Table 1.**  
Patient demographics and pathological characteristics

	No. (%)
Ethnicity:	
White	184 (76.3)
Hispanic	19 (7.9)
Black	14 (5.8)
Asian	5 (2.1)
Other	19 (7.9)
Sex:	
Male	175 (72.6)
Female	66 (27.4)
Comorbidities:	
Hypertension	164 (68)
Tobacco	100 (41)
Coronary artery disease/history of myocardial infarction	96 (39.8)
Hyperlipidemia	90 (37.3)
Diabetes mellitus	89 (37)
Chronic renal insufficiency	66 (27.4)
2nd Malignancy	61 (25.3)
Obesity	46 (19.1)
Atrial fibrillation	35 (14.5)
Chronic obstructive pulmonary disease	1 (0.4)
IUFS:	
0	4 (1.7)
1 Side only	2 (0.8)
1/Side	179 (72.3)
2 or More sides	56 (23.2)
Pathological stage:	
CIS	39 (16.2)
pT0	15 (6.2)
pTa	7 (2.9)
pT1	31 (12.9)
pT2	36 (14.9)
pT3	76 (31.5)
pT4	37 (15.4)
Low	48 (20)
Lymph node status:	
N0	157 (65.1)
N1	28 (11.6)
N2	47 (19.5)
Nx	9 (3.8)
Pathological grade:	
High	193 (80)
CIS	184 (76.3)
Lymphovascular invasion	117 (48.5)

complications were compared among single vs multiple rounds of IUFS using the chi-square test for categorical variables and Student's t-test for continuous variables. Oncologic outcomes measured included UTR, metastasis, DSS and OS. Upper tract recurrence was defined as endoscopic, radiographic or pathologically proven recurrence in the ureter or kidney after radical cystectomy. Predictors of these outcomes were analyzed with Cox proportional hazards, along with permanent section margin status (ureter and bladder), ureteral orifice involvement on final pathology, pathological stage and grade, pathological lymph node status, presence of CIS and lymphovascular invasion, adjuvant chemotherapy, patient comorbidities and postoperative complications. The Kaplan-Meier method was used to compare positive vs negative IUFS and section conversion to negative vs negative for each of the oncologic

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