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Diagnostic accuracy of intraoperative frozen sections during radical cystectomy does not affect disease-free or overall survival: a study of 364 patients with urothelial carcinoma of the urinary bladder☆

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ABSTRACT

The utility of intraoperative frozen sections for determining ureteral and urethral margin status is controversial. In this study, we evaluated the sensitivity and specificity of frozen section diagnosis with the corresponding final tissue diagnosis in a series of 364 patients undergoing radical cystectomy for urothelial carcinoma of the urinary bladder. Multiple definitions of a positive diagnosis were analyzed. We then used clinical follow-up data to determine the effect of various frozen section diagnoses, frozen/permanent section discordance, and surgical margins on overall survival and disease-free survival. Increasing severity of dysplasia was associated with corresponding increases in positive likelihood ratio, with carcinoma displaying the highest positive likelihood ratio (211.43) for an accurate frozen section diagnosis. A diagnosis of carcinoma on frozen section did not affect overall or disease-free survival nor did a positive surgical margin. Frozen/permanent discordance did not show significant associations with overall survival or disease-free survival. The lone variable approaching statistical significance was an association between frozen/permanent discordance of ureteral samples and disease-free survival (hazard ratio, 3.23; $P = .07$; multivariate Cox proportional hazards model). The results of this study, the first to evaluate the use of different cutoffs for a positive diagnosis and the effects of frozen/permanent discordance, do not support the routine use of intraoperative frozen section during radical cystectomy for urothelial carcinoma. However, subgroups at high risk for positive ureteral margins may benefit from intraoperative frozen section evaluation.

1. Introduction

In 2014, there were 74 690 estimated new cases and 15 580 deaths attributed to bladder cancer in the United States [1]. Radical cystectomy is the standard treatment for patients with bladder cancer who have muscle-invasive disease or have failed conservative treatments [2]. Surgeons make the decision to evaluate margins intraoperatively on a case-by-case basis, and there is much debate in the literature concerning the utility of intraoperative frozen sections for determining ureteral and urethral margin status [3-22].

Pathologic evaluation of frozen sections of the urinary tract can result in a wide variety of classifications including "benign/negative for malignancy"; "atypia"; "focal, mild, or moderate dysplasia"; "severe, marked, or high-grade dysplasia"; "carcinoma in-situ (CIS)/noninvasive carcinoma"; and "invasive carcinoma." Previous studies have not used a consistent definition of what constitutes a "positive" margin. Most studies have defined carcinoma as positive and moderate dysplasia or less as "negative"; however, there is no consensus on how to classify severe dysplasia and CIS [3,6-8,10-12]. In fact, a recent study considered any diagnosis other than normal epithelium (ie, atypia, dysplasia, CIS, or urothelial carcinoma) as positive [4]. Thus, a positive or negative margin has been designated by convention rather than by empirical evidence determining the proper definition of a positive margin on the spectrum of benign to carcinoma.

In this study, we evaluated the accuracy of intraoperative frozen sections compared to the corresponding final tissue diagnosis determined on permanent sections in a series of 364 patients undergoing radical cystectomy for urothelial carcinoma of the urinary bladder. We used 4 cutoffs ("mild dysplasia," "moderate dysplasia," "severe dysplasia/CIS," and "carcinoma") to consider a margin positive to calculate the sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (−LR) for each cutoff. Using the optimal cutoff for a positive diagnosis, we identified discordant cases, defined as a disagreement between the diagnosis on frozen section and the diagnosis on the corresponding permanent section. We then used clinical follow-up data to determine the effect of various frozen section diagnoses and frozen/permanent section discordance on overall survival and disease-free survival.

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2. Materials and methods

2.1. Patients

The study sample consisted of 465 patients who underwent radical cystectomy for bladder cancer at Loyola University Medical Center from 2000 to 2012. Patients were identified using a natural language query for the term *radical cystectomy* in the pathology database. Exclusion criteria included radical cystectomy for indications other than urothelial carcinoma of the bladder, cases of urothelial carcinoma with any amount divergent differentiation, and cases in which incomplete data from surgical and pathology reports prevented accurate classification of clinical stage. After applying exclusion criteria, 364 patients were included in the study.

2.2. Definition of end points

In accordance with current guidelines [23], *recurrence of disease* was defined as evidence of a positive histologic, cytologic, clinical, or radiologic result reported in the clinical notes. Disease-free survival was calculated as the time from radical cystectomy to the date of the first documented clinical recurrence or until last follow-up if the patient had not experienced a clinical recurrence. Patients with no documented recurrence were censored at time of death or at date of last follow-up visit. Survival was calculated as the time from cystectomy to the date of death; all deaths, regardless of cause, were counted as events. The Social Security Death Index and published obituaries were used to investigate survival status as of July 1, 2013. Patients who were not deceased as determined by the Social Security Death Index and published obituaries were censored at the date of last follow-up visit. Patients were considered lost to follow-up if they had not been seen within 1 month of the urologist's recommended return to clinic and were not deceased as determined by the Social Security Death Index and published obituaries.

2.3. Definition of variables

Age was determined using the patient's age at the time of radical cystectomy. Tumor size (T) and lymph node involvement (N) were taken from the gross pathologic description. Depending on the standard definitions used at the time of operation, T and N were defined using either the 1997 American Joint Committee on Cancer bladder cancer staging definitions [24] (for patients operated before 2011) or the 2010 American Joint Committee on Cancer bladder cancer staging definitions [25]. The 4 changes in the 2010 guidelines compared to the 1997 guidelines are as follows: (1) size is no longer relevant to N staging, (2) the common iliac nodes are considered to be a secondary drainage region representing N3 rather than M1 disease, (3) T4 disease includes prostatic stromal invasion but not subepithelial invasion of the prostatic urethra, and (4) tumors are graded as low or high grade rather than with a 4-grade system. Per our institution's conventions, surgical margin status was defined as positive if the permanent section of the surgical margin had a diagnosis of "carcinoma/CIS." Tumor extension was classified as positive if there was a diagnosis of carcinoma/CIS on any of the permanent sections of the urethra or ureters. Finally, *frozen/permanent discordance* was defined as a frozen section diagnosis different than the corresponding permanent section.

2.4. Statistical analysis

Univariate analysis was performed using Kaplan-Meier curves for categorical variables and Cox proportional hazards modeling for continuous variables. *Positive likelihood ratio* was defined as sensitivity/1 − specificity. *Negative likelihood ratio* was defined as 1 − sensitivity/specificity. Variables with a nominal *P* value of less than .10 in univariate analysis were included in the initial multivariate model. Stepwise elimination of nonsignificant variables was performed, and the final model included all significant covariates in addition to the variable of interest (frozen/permanent discordance, frozen section carcinoma, and positive surgical margin). Hazard ratios (HRs), 95% confidence intervals (95% CI), and *P* values were calculated for each variable. The proportional hazards assumption was tested for each variable included in the final model by assessing the significance of a ln(time) * variable interaction term. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC). Significance for all tests was set at $P \leq .05$ with the exception of the initial univariate analyses, as mentioned above.

3. Results

The study cohort consisted of 364 urothelial cancer patients with an average age of 67.9 years (range, 34-88 years) and was 75.8% male (Table 1). Most tumors (98.4%) were high-grade urothelial carcinomas as defined by the 1998 World Health Organization/International Society of Urological Pathology consensus conference [26], later incorporated into the World Health Organization classification of bladder tumors [27]. Of the 465 patients in the original cohort, 65 underwent radical cystectomy (RC) for reasons other than bladder cancer, and 7 had missing data preventing further analysis. Twenty-nine patients had nonurothelial bladder cancers, including 7 adenocarcinomas, 13 squamous cell carcinomas, 9 with other histology types including neuroendocrine carcinomas and sarcomas. One hundred seventy-three deaths occurred during the follow-up period with a median interval of 20 months (range, 1-120 months) from cystectomy. Disease recurrence was documented in 88 patients after an interval of 14 months (range, 0-65 months) from cystectomy. The distributions of frozen section and permanent section diagnoses are presented by tissue type in Table 2.

Table 1
Patient characteristics

No. of patients	364
Age (years ± SD)	67.9 ± 10.3
Male sex	276 (75.8%)
Histologic grade	
Low	5 (1.6%)
High	304 (98.4%)
Pathologic stage	
pT_{IS}	47 (13.1%)
pT1	62 (17.3%)
pT2	88 (24.5%)
pT3	119 (33.1%)
pT4	43 (12.0%)
Nodes	
pN0	261 (76.5%)
pN1	34 (10.0%)
pN2	40 (11.7%)
pN3	6 (1.8%)
Positive final margin (%)	
Left ureter	12 (3.8%)
Right ureter	14 (4.4%)
Urethra	14 (4.6%)
Any margin	33 (10.7%)
Positive extension (%)	
Left ureter	46 (14.6%)
Right ureter	41 (13.0%)
Urethra	53 (16.9%)
Any extension	93 (30.3%)
Deaths (all-cause mortality)	173 (48.1%)
Recurrences	88 (25.9%)
UUT recurrences	10 (2.7%)
Lost to follow-up	129 (35.4%)
Chemotherapy	101 (28.5%)
Additional primary cancer or transplant patient	120 (34.8%)
Median time to death (mo)	20 (0-120)
Median time to recurrence (mo)	14 (0-65)
Median time to most recent visit (mo)	26 (0-156)