



Original article

Accuracy of urethral frozen section during radical cystectomy for bladder cancer

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Abstract

Objective: Our objective was to determine the accuracy of urethral frozen section (FS) by analyzing our clinical experience.

Materials and methods: A total of 298 patients undergoing radical cystectomy for bladder cancer with benign or malignant urethral FS were identified between 2000 and 2012. Urethral FS were compared with rereviewed FS to calculate the positive and negative predictive values of the FS. To assess the ability of the positive FS to be cleared with further sampling/resection, FS were then compared with the final urethral margin. The cases of positive urethral FS were then specifically analyzed to assess rates of urethral recurrence and survival.

Results: All negative FS were confirmed to be negative on FS rereview and on final pathology, resulting in a NPV of 100%. Urethral FS were positive in 28 (8.7%) patients, of whom 2 (7%) were negative on FS rereview, yielding a positive predictive value of 93%. Both false positives were because of contamination of detached cancer from the bladder being present in the FS. After additional sampling/resection, the final margin was negative in 13 (46%) patients.

Conclusions: A negative urethral FS reliably identifies individuals for whom urethrectomy is unnecessary and provides robust information for decision-making regarding the safety of orthotopic reconstruction. Nearly half of the patients with a positive FS were ultimately determined to have a negative final margin. Accordingly, we recommend that surgeons and pathologists discuss positive FS findings at the time of surgery and consider whether additional tissue should be analyzed in real time. © 2016 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Frozen section analysis

1. Introduction

Of the estimated 74,000 new cases of bladder cancer in 2015, 25% to 30% would present with muscle-invasive disease and require surgical excision [1]. Radical cystectomy with lymphadenectomy is the standard of care for surgical cure. Urethral frozen sections (FS) have been long used intraoperatively to assess the extent of disease to

determine if the patient is a candidate for an orthotopic neobladder reconstruction. Although the presence of urothelial cancer in the prostate in men and bladder neck in women constitute relative contraindications to orthotopic reconstruction, a positive urethral FS has been considered a strict indication to perform cutaneous diversion [2,3].

Additionally, FS may be used to decide whether the patient should undergo simultaneous urethrectomy at the time of cystectomy. Of all men undergoing cystoprostatectomies, 8.1% would ultimately undergo a urethrectomy, of whom more than half would undergo simultaneous or

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staged procedures (with the remainder occurring after urethral recurrence) [4]. Although some have advocated for simultaneous urethrectomy when the urethral margin FS is positive, this topic remains controversial [5–8].

Despite the fact that obtaining urethral FS represents the contemporary standard of care, few studies have assessed its diagnostic accuracy. As a result, using a retrospective cystectomy cohort we sought to determine the value of urethral FS in choosing orthotopic reconstruction and the need for urethrectomy. It is currently unknown whether a negative urethral FS predicts a benign urethra in all cases, an important factor when evaluating a patient for orthotopic diversion. Similarly, it is also unclear whether a positive urethral FS accurately predicts true cancer at the urethral margin, an equally important determinant in the decision to perform urethrectomy. Our objective was thus to determine the accuracy of urethral FS in a retrospective cohort of 750 consecutive patients undergoing radical cystectomy during which urethral FS was often performed.

2. Materials and methods

We retrospectively identified consecutive patients with bladder cancer who underwent a radical cystectomy from 2000 to 2012 in our institutional review board–approved, institutional urothelial cancer registry. The cohort included patients of all clinical stages and all histologic subtypes. Within this cohort, we selected those cases in which FS had been performed to assess distal urethral margins.

Our institutional protocol for FS preparation has been previously described [9]. In brief, the tissue of interest was embedded in optimum cutting temperature medium and frozen. Overall, 2 sections were then cut, placed on a glass slide, and stained with hematoxylin and eosin for pathology review. At least 2 levels are cut per sample. Owing to the difficulty of FS analysis, it is our institution's policy that a genitourinary pathologist review all urethral FS; as a result, more than 95% of FS diagnoses were rendered by 2 genitourinary pathologists. After the FS is complete, the optimum cutting temperature medium is melted and then the tissue is formalin-fixed overnight, embedded in paraffin wax, cut, placed on a slide with hematoxylin and eosin staining. This is referred to as the “frozen section control.” Cases where there is a discrepancy between the FS and the FS control triggers a rereview of the FS. This is hereby referred to as the “frozen section rereview.” If a FS is deemed positive, in many cases the surgeon will take a more distal urethral margin for permanent section. This specimen is referred to as the “final urethral margin.” It should be noted that it is not the author's routine practice to randomly sample the urethra before receiving neoadjuvant chemotherapy (NAC) or cystectomy; rather, urethral sampling is only performed in the setting of a urethra suspicious for tumor or a high-grade positive cytology of undetermined etiology. Additionally, in our series patients with a positive

FS underwent additional tissue excision and cutaneous urinary diversion.

Covariates of interest included both patient (age, race, and sex) and tumor (stage and grade) related variables, as well as the patient's NAC status. The primary outcomes were the negative predictive values (NPV) and positive predictive values (PPV) of urethral FS compared with FS rereview, which reflect the accuracy of FS as a diagnostic modality. Additionally, we compared the FS to the final urethral margin, which reflects the rate at which the positive FS can be cleared of cancer either by taking the primary FS itself or after further sampling/resection. Secondary outcomes of interest were the rates of urethral recurrence and overall survival among patients with a positive urethral FS.

2.1. Statistical analysis

Baseline characteristics of patients who had frozen margins sent were assessed. Continuous variables were compared with the Wilcoxon rank-sum test and categorical variables with Fischer exact test or the chi-square test. To assess for collinearity between a positive frozen urethral margin and advanced T stage (pT2+) or positive final urethral margin and advanced T stage, we calculated the variance inflation factor (VIF). A VIF <2 was considered acceptable. No collinearity was observed between final urethral margin and stage (VIF = 1.00) and urethral FS and stage (VIF = 1.01).

The FS on the urethral margin was compared with the FS rereview and to the final urethral margin. The sensitivity and specificity as well as the PPV and NPV were calculated. The cases of positive urethral FS were then specifically analyzed to assess rates of bladder cancer recurrence, bladder cancer–specific death, and overall death. Differences in overall survival between those with a positive and negative urethral FS were assessed with Cox proportional hazards model. All statistical analyses were performed with Stata 13 (StataCorp, College Station, TX). A $P < 0.05$ was considered statistically significant for all the tests.

3. Results

In all, 750 patients with complete pathologic information underwent cystectomy for bladder cancer at our institution during this 12-year period (median follow-up = 36.9 mo). Urethral FS were sent in 322 (43%) cases. Patients with urethral FS sent were more likely to be younger (mean age = 61 vs. 68 y, $P < 0.001$) with less pT4 pathologic stage disease ($P = 0.01$; Table 1). They were also more likely to receive NAC (22.7% vs. 16.8%, $P = 0.04$). However, there were no differences in the rate of positive FS among patients receiving NAC ($P = 0.6$).

Prior work from our institution has demonstrated that the majority (84%–95%) of “atypia” and “denudation” in the

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