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SHORT COMMUNICATION

The Impact of Routine Frozen Section Assessment During Penectomy on Surgical Margin Status and Long-Term Oncologic Outcomes

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Abstract

No recent studies have focused on assessing the role of intraoperative frozen section assessment (FSA) in the status of surgical margins (SMs) relating to the outcomes of penectomy cases. In this study, we investigated the utility of routine FSA of the SMs in men undergoing penectomy. A retrospective review identified consecutive patients who underwent partial ($n = 26$) or total ($n = 12$) penectomy for penile squamous cell carcinoma at our institution from 2004 to 2015. FSA of the SMs was performed in 21 (80.8%) partial and 10 (83.3%) total penectomies. FSAs were reported as positive ($n = 3$, 9.7%), atypical (n = 3, 9.7%), and negative ($n = 25$, 80.6%). All of the positive or negative FSA diagnoses were confirmed accurate on the frozen section controls, whereas the 3 cases with atypical FSA had non-malignant, atypical, and carcinoma cells, respectively, on the controls. Final SMs were positive in 6 (15.8%) penectomies, including 4 (12.9%) FSA cases versus 2 (28.6%) non-FSA cases ($P = 0.569$). Furthermore, initial positive (1 of 3) and atypical (3 of 3) FSA cases achieved negative conversion by excision of additional tissue sent for FSA. Kaplan-Meier analysis revealed that performing FSA or its number/diagnosis was not significantly associated with disease progression. Thus, performing FSA during penectomy does not appear to have any significant impact on final SM status nor long-term oncologic outcomes. However, as seen in at least 4 cases, select patients may benefit from the routine FSA.

Keywords Frozen section assessment · Penile cancer · Penectomy · Prognosis · Surgical margin

Introduction

Penile cancer is a relatively rare malignancy in developed countries, while an increase in its incidence has been reported in some regions of low socioeconomic status [1, 2]. Despite advances in multimodal therapy, partial or total penectomy remains the standard care for men with localized penile squamous cell carcinoma. Meanwhile, the status of final surgical margins (SMs) is a critical prognosticator in those undergoing penectomy for penile cancer [2, 3].

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Intraoperative frozen section assessment (FSA) of biopsy or resection specimens often provides critical information for appropriate surgical management. FSA of the SMs during urological surgery was also found to be useful at least in select patients (*e.g.* Gleason score 7 prostate cancer, pT1a exophytic renal tumor) [4–6]. However, to the best of our knowledge, there are no recent studies focusing on assessing the role of FSA in the status of SMs relating to the outcomes of penectomy cases. Instead, a few review articles do not highly recommend its use in the assessment of SMs during penectomy, mainly because lesions often show well differentiated squamous proliferation that can mimic non-neoplastic conditions [6, 7]. The current study aimed to investigate the utility of routine FSA of the SMs in men undergoing penectomy for squamous cell carcinoma.

Materials & Methods

We studied consecutive patients with penile squamous cell carcinoma who had undergone penectomy at our institution

between June 2004 and December 2015. From our surgical pathology electronic database, we identified 38 cases coded as partial ($n = 26$) or total ($n = 12$) penectomy specimens. The decision to send tissue for FSA was entirely at the discretion of the surgeon. Intraoperative FSA of the SMs was then correlated with the diagnosis of the frozen section control as the permanent section of the remaining tissue, the status of final SM, and patient outcomes. Cases with FSA evaluating any other non-margin related tissue were considered to have no FSA performed.

Data was analyzed, using the Student's *t*-test for continuous variables and Fisher's exact test for non-continuous variables. The rates of recurrence-free survival were calculated by the Kaplan-Meier method and comparison was made by log-rank test. *P* values less than 0.05 were considered to be statistically significant.

Results

FSA of the SMs was performed in 21 (80.8%) partial penectomies and 10 (83.3%) total penectomies, while no FSA was done for SMs in other 7 (18.4%) cases. Table 1 summarizes the clinicopathologic features of the patients with ($n = 31$; 81.6%) and without ($n = 7$; 18.4%) intraoperative FSA. Between these two cohorts, there were no statistically significant differences in age of the patients, tumor size, tumor grade/differentiation, pT stage, pN stage, and lymphovascular invasion. Final SMs were positive in 6 (15.8%) penectomies (3 partial and 3 total), including 4 (12.9%) FSA cases versus 2 (28.6%) non-FSA cases ($P = 0.569$). Similarly, only in men undergoing partial penectomy, final SMs were positive in 2 (9.5%) of 21 FSA cases versus 1 (20.0%) of 5 non-FSA cases ($P = 0.489$).

Figure 1 depicts the outcomes of the 31 FSA cases. FSAs were reported as positive ($n = 3$, 9.7%), atypical (n = 3, 9.7%), and negative ($n = 25$, 80.6%). All of the positive or negative FSA diagnoses, including those in 10 cases with well differentiated carcinoma, were confirmed accurate on the frozen section controls, whereas the 3 cases with atypical FSA had non-malignant, atypical, and carcinoma cells, respectively, on the controls. In addition, 1 of 3 initial positive FSA and 3 of 3 initial atypical FSA cases achieved negative conversion by excision of additional tissue sent for FSA. By contrast, 2 FSA-negative cases showed carcinoma at the final SM where FSA was not submitted or sampled. Thus, 4 patients showing final positive SMs included 1 initially FSA-positive case (re-excision sent only for a permanent section which was positive), 1 initially FSA-positive case (re-excision sent for FSA which was negative; SM-positive elsewhere), and 2 initially FSA-negative cases (SM-positive elsewhere).

During follow-up (mean: 38.0; median: 27; range: 1–137 months), 5 patients, including 4 FSA-negative/final SM-negative and 1 FSA-positive/final SM-positive cases, developed tumor recurrence. Only one of the patients died of penile cancer. Kaplan-Meier analysis coupled with log-rank test was then performed to assess the role of FSA in oncologic outcomes. Overall, performing FSA did not considerably affect recurrence-free survival (Fig. 2a). No impact of the number (Fig. 2b-c) or diagnosis (Fig. 2d) of FSA on patient outcomes was also seen. Meanwhile, patients with positive SM tended to have a higher risk for disease recurrence, compared with those with negative SM (Fig. 2e).

Table 1 Clinicopathologic profile of patients undergoing penectomy for penile squamous cell carcinoma

Patient characteristics	FSA performed	FSA not performed	*P* value
Number of patients (%)	31 (81.6%)	7 (18.4%)	
Age (mean, year)	70.0	75.1	0.304
Type of surgery			1.000
Partial penectomy	21 (67.7%)	5 (71.4%)	
Total penectomy	10 (32.3%)	2 (28.6%)	
Tumor size (mean, cm)	4.10	3.18	0.519
Tumor grade			0.566
Well differentiated	10 (32.2%)	4 (57.1%)	
Moderately differentiated	13 (41.9%)	2 (28.6%)	
Poorly differentiated	8 (25.8%)	1 (14.3%)	
pT			0.336
pTa or pTis	2 (6.5%)	1 (14.3%)	
pT1	14 (45.2%)	3 (42.9%)	
pT2	7 (22.6%)	3 (42.9%)	
pT3	8 (25.8%)	0 (0%)	
pN			NA
pNx	31 (100%)	7 (100%)	
Lymphovascular invasion			0.340
Absent	23 (74.2%)	6 (85.7%)	
Indeterminate	2 (6.5%)	1 (14.3%)	
Present	6 (19.4%)	0 (0%)	
Final surgical margins			0.569
Negative	27 (87.1%)	5 (71.4%)	
Positive	4 (12.9%)	2 (28.6%)	

Discussion

Intraoperative FSA of the SMs is often a standard procedure in various radical surgeries for solid tumors. Indeed, intraoperative pathology consultation has often been requested for the assessment of the SM status during penectomy, especially partial resection of the penis for carcinoma. Several review articles have recommended FSA of the entire circumference of the amputation margin particularly in partial penectomy because penile cancer can extend through the penile skin,

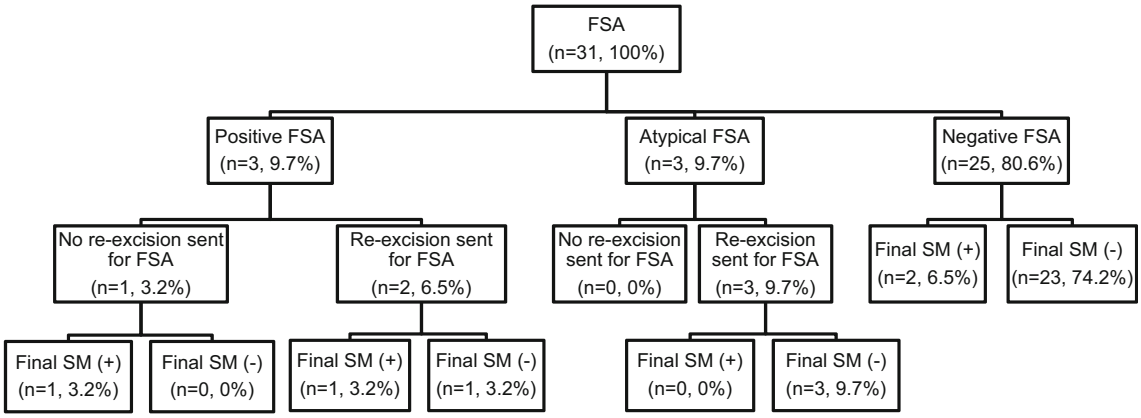

Fig. 1 Flow diagram for 31 cases with FSA

the corpus spongiosum, the corpora cavernosa, and the urethral mucosa [7, 8]. However, there appear to be no studies comparing its benefit in penectomy cases with versus without FSA. We therefore attempted to determine the utility of FSA for SMs during penectomy.

Again, no existing literature has provided clinical data readily indicating a significant benefit of FSA in men with penile cancer in terms of the risk of incomplete resection and subsequent tumor recurrence. In a relatively large cohort of 179 patients with penile cancer in whom FSA was not undergone from a single institution, 22 (12.3%) were found to have a positive SM, and the overall 5-year local recurrence-free survival rate was 86.3% [3]. By contrast, in studies where FSA of the SMs was routinely performed, the rates of positive SMs and postoperative tumor recurrence were reported to be 0–6% and 4–10%, respectively [9, 10]. Our current study is unique in that it contains patients who did not undergo FSA of SMs during penectomy, allowing for the comparison of performing versus not performing FSA. We thus found that intraoperative FSA did not noticeably reduce the incidence of positive SMs (28.6% ➔ 12.9%) nor improve 5-year recurrence-free survival (100% ➔ 85.1%). However, in 4 of 6 cases

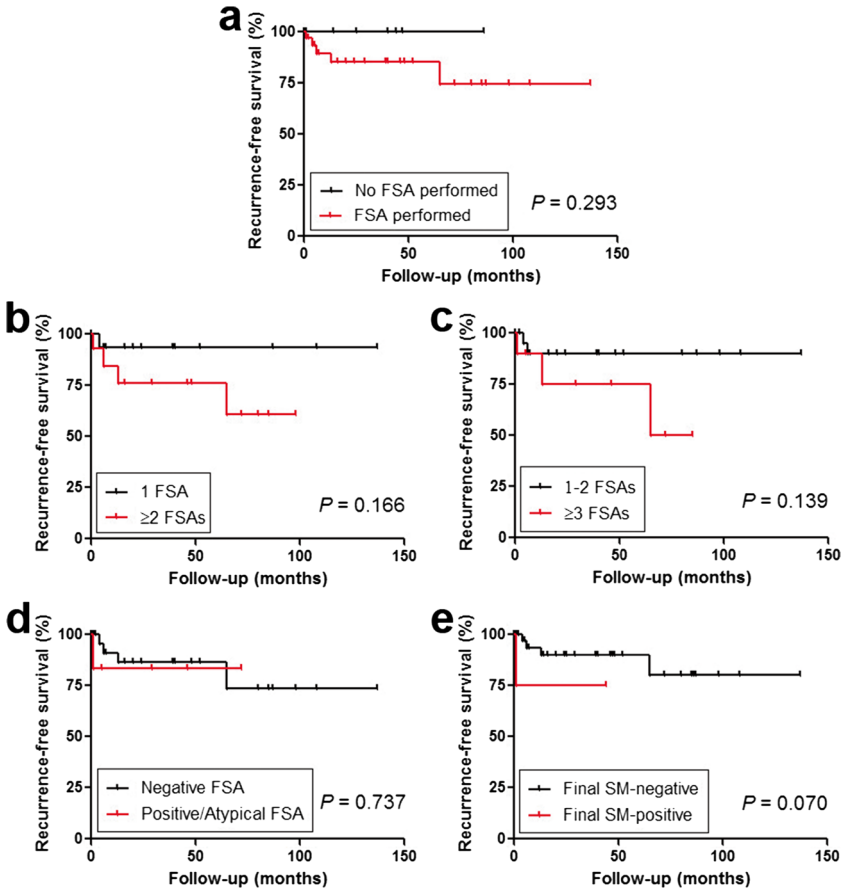

Fig. 2 Recurrence-free survival stratified by cases with *vs.* without FSA (**a**), 1 *vs.* 2 or more FSAs (**b**), 1–2 *vs.* 3 or more FSAs (**c**), initial negative *vs.* positive or atypical FSAs (**d**), and negative *vs.* positive final SMs (**e**). FSA of re-excision in initial positive or atypical FSA cases was not counted

with initial positive or atypical FSA, negative conversion was achieved by excision of additional tissue.

As aforementioned, it is often difficult to morphologically distinguish between well differentiated squamous cell carcinoma and non-neoplastic conditions in penile tissues sent for intraoperative consultation [6, 7]. However, the diagnostic accuracy of FSA of the SMs during penectomy is not well-documented. In our cases, FSA correctly identified benign and malignant lesions at the SMs, including those in 10 cases with well differentiated carcinoma, while the 3 cases with atypical diagnosis showed benign, atypical, and carcinoma cells, respectively, on the frozen section controls. As suggested [7], close communication between the surgeon and pathologist is critical for the assessment of penectomy specimens.

Our study has methodological limitations. In particular, due to its retrospective design, we cannot definitively exclude a possible confounding effect of surgeon preference or case complexity on the decision to perform or not perform FSA during penectomy. Thus, there might be a selection bias in our cases with and without FSA, although no statistically significant differences in their clinicopathologic profile were observed in the two groups. In addition, the number of the FSA group is relatively small. Larger prospective studies are thus warranted to verify our results. A cost/benefit analysis regarding the use of routine FSA for penectomy may also be useful to explore the economic ramifications of this practice.

In conclusion, performing FSA during penectomy does not appear to have any significant impact on final SM status nor long-term oncologic outcomes. However, as seen in at least 4 cases, select patients may benefit from the routine FSA. Meanwhile, diagnostic accuracy of FSA of the SMs was found to be quite high. Furthermore, final positive SM tended to correlate with the risk of disease progression.

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