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The utility of intraoperative retroareolar margin frozen section assessment and the management of atypical epithelial proliferative lesions at the retroareolar margin in nipple-sparing mastectomies

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ABSTRACT

Objectives: Nipple-sparing mastectomy (NSM) has become more frequently utilized due to superior psychological and cosmetic outcomes. The aim of this study was to evaluate the accuracy and utility of intraoperative frozen section evaluation of the retroareolar margin (RAM) in NSM. The management of atypical epithelial proliferative lesions at the RAM was also reviewed and discussed.

Methods: A single institution, retrospective analysis was performed on all therapeutic NSM patients with intraoperative evaluation of the RAM from 2014 to 2018. Patient demographics, tumor characteristics, pathologic assessment of the RAM, surgical management, and clinical follow-up were reviewed.

Results: Seventy-four nipple-sparing mastectomies with intraoperative evaluation of RAMs were identified. Concordance was 95% between frozen and permanent section diagnoses with 4 cases representing false negatives and no false positives. There were no instances of nipple-areolar complex (NAC) recurrence in all cases with preserved NACs (mean follow up: 750 days). In the 9 cases where NACs were excised based on intraoperative RAM evaluation, the findings in the excised NACs were negative in 6 and ductal carcinoma in situ in 3 cases. Postoperative measurement of the tumor to nipple distance was the only statistically significant variable associated with a positive RAM by multivariable logistic regression (OR 0.475; 95% CI 0.238–0.946).

Conclusions: Intraoperative RAM evaluation demonstrated high concordance with permanent histology. Negative RAM, including atypical epithelial proliferative lesions, led to NAC preservation without recurrence. Positive RAM alone did not predict NAC involvement, although pagetoid spread of ductal carcinoma in situ along nipple ducts may predict NAC positivity.

1. Introduction

Nipple-sparing mastectomy (NSM) has become more frequently utilized in the surgical treatment of breast cancer due to improved cosmetic outcomes, psychosocial well-being, and patient satisfaction [1,2]. Analysis of the National Surveillance, Epidemiology, and End Results database demonstrated a 7-fold increase in reported NSMs performed between 2009 and 2013 [3].

Numerous studies have demonstrated the oncologic safety of NSMs for prophylactic, risk-reduction, and therapeutic mastectomies [3-9]. Recent meta-analysis of studies with follow-up intervals greater than 5 years reported overall survival, disease-free survival, locoregional recurrence (LR), and nipple-areolar complex (NAC) recurrence of 86.8%, 76.1%, 11.4% and 3.4%, respectively, with no statistically significant difference when compared to skin-sparing mastectomy or modified radical mastectomy [10]. However, several factors within the current body of literature limit its generalizability for routine practice, including lack of reporting and/or variability in patient selection criteria, surgical technique, pathologic processing, and management of retroareolar margin (RAM) specimens [11].

Not all institutions routinely utilize intraoperative frozen section (FS) evaluation of the RAM, relying instead on permanent histology and subsequent NAC excision during staged reconstruction [12,13]. Although this practice eliminates the risk of false positive intraoperative diagnoses leading to unnecessary NAC excision, it may necessitate additional procedures, delayed reconstruction, and unnecessary stress

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and anxiety for patients. For institutions that do routinely utilize RAM FS, it is imperative that pathologic processing and interpretation is optimized for consistency and diagnostic accuracy.

Review of recent studies reveals significant heterogeneity in pathology protocols and practice, particularly with respect to the classification and management of atypical epithelial lesions [12-19]. Reports often treat these lesions as de facto negative, without specifying their prevalence or subsequent management. Alternatively, these lesions may be lumped into a single "atypical" category, which is managed as a positive margin, or split to include LCIS as positive and other forms of atypia as negative.

This study aims to review our experience in utilizing intraoperative frozen sections to assess retroareolar margins in nipple-sparing mastectomies. We will share our protocol, analyze discordant cases, and propose ways to improve. The management and follow up of cases with findings of atypical epithelial proliferative lesions including atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and lobular carcinoma in-situ (LCIS) at the RAM are reviewed and discussed.

2. Materials and methods

2.1. Case selection

This single-institution, retrospective study was approved by our Institutional Review Board. A natural language search of our pathology information system provided a list of consecutive NSMs performed at our institution from 2014 to 2018 (inclusive). Prior to 2014, NSMs were rarely performed at our institution (a total of 4 NSMs during 2010–2013). All cases were screened to exclude prophylactic or risk-reduction NSMs, non-breast primary tumors, resection specimens without residual disease, and cases for which FS of the RAM was not performed. Information including patient demographics, tumor characteristics, pathologic assessment of the RAM, surgical management, and clinical follow-up were collected.

Patients are eligible for NSM based on preoperative imaging and physical exam evaluation. Invasive or in situ disease must be at least 2 cm from the NAC. Breast size and degree of ptosis is also considered for length of flaps, NAC perfusion, and optimal cosmetic outcome.

2.2. Specimen collection

The RAM is sent for FS diagnosis as a thin shave of subareolar tissue by the surgeon, or the intact mastectomy specimen is delivered with surgical staples outlining the subareolar tissue, from which a thin shave of tissue is procured by the pathology assistant. The shave of subareolar tissue is embedded *en face* and a minimum of 3 levels are stained with hematoxylin and eosin for on-site evaluation. The remaining RAM tissue is processed for permanent histology. Ancillary studies are performed at the discretion of the pathologist. In accordance with standard practice, the surgeons and pathologists are not blinded to previous diagnoses or clinical history.

2.3. Data collection

All recorded patient data reflects patient status at the time of their most recent follow up at our institution, or outside institutions for which shared records were available, as of December of 2019. For cases of bilateral NSM, each breast specimen and each RAM FS were treated independently for statistical analysis. Only invasive disease and ductal carcinoma in situ (DCIS) were considered "positive" for both FS and permanent histology in calculating diagnostic accuracy. All other diagnoses were categorized as atypical epithelial proliferative lesions, including LCIS, ALH, and ADH. Slides were retrospectively reviewed only for cases that did not have a clear categorical diagnosis on the original FS report and upon re-review were assigned to a defined entity. For example, a case designated "atypical epithelial proliferation" was reviewed and assigned to the ADH category.

Table 1
Patient demographic information and tumor characteristics (N=74).

Characteristics	Mean (range) or %
Age (years)	49 (30–76)
Largest tumor focus (cm)	
Invasive mammary carcinoma	1.2 (0.1–4.3)
Ductal carcinoma in situ	1.5 (0.1–5)
Closest tumor to nipple-areolar complex	
Radiologic preoperative measure (cm)[a]	4.0 (1.1–12)
Pathologic postoperative measure (cm)	3.0 (0.1–8)
Length of follow up (days)	703 (123–2071)
Tumor multifocality present	34.2
Invasive histology	
Ductal	89.1
Lobular	16.4
Mucinous	3.6
Highest invasive grade[b]	
1	18.5
2	63.0
3	18.5
Ductal carcinoma in situ present	77.0
Lymphovascular invasion present	13.3
Marker status	
Luminal A or B	70.0
Her2 enriched	18.3
Triple negative	11.7
Primary tumor staging[c]	
Tis	26.0
T1	52.1
T2	21.9
Lymph node staging[c]	
N0	85.1
N1	12.2
N2	2.7
Neoadjuvant chemotherapy received	27.0
Adjuvant chemotherapy received	16.2
Post-mastectomy radiation therapy	10.8

[a] MRI when available (otherwise ultrasound/mammography).
[b] Elston-Ellis modified histologic grading [20].
[c] 8th Edition, AJCC Staging Manual [21].

2.4. Statistical analysis

Diagnostic accuracy was calculated by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and concordance rate. Confidence intervals were calculated for sensitivity and specificity by the Clopper-Pearson exact method. Associations between RAM status and categorical variables were examined using Chi-square or Fisher's exact test. Interval-based variables were evaluated using the two-sample t-test. Both the Shapiro-Wilk test and visual evaluation were carried out for determining data distribution. Multivariable logistic regression analysis was performed to estimate the probability of positive/atypical RAM diagnoses while taking independent variables and confounding into consideration. A p value of less than 0.05 was pre-specified for statistical significance. All statistical analysis was performed using SAS 9.4.

3. Results

3.1. Case characteristics and management

Following exclusion, the database search returned 74 consecutive NSMs. Bilateral NSM was performed on 3 patients. All patients were female, and the mean age was 49 years (range 30–76). Table 1 details patient population demographic information and tumor characteristics.

Among the 74 NSMs, 59 cases had concordant intraoperative FS and permanent section diagnoses of negative RAMs, of which 56 NACs were preserved. Subject selection and disposition are summarized in Fig. 1. Three NACs in this group were excised due to various reasons and all

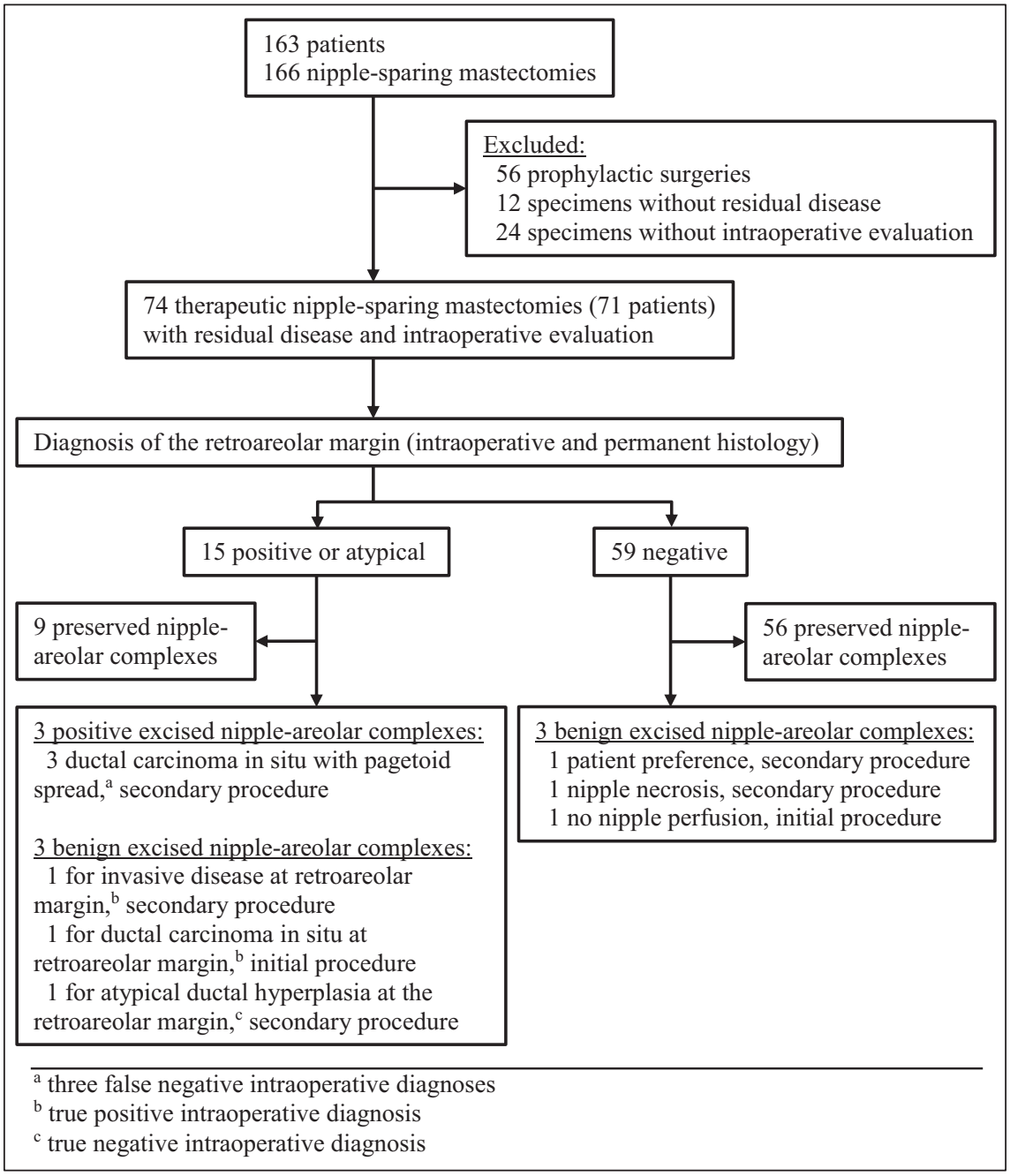

Fig. 1. Flow diagram of subject selection and nipple-areolar complex management.

showed benign histology. Fifteen cases had positive or atypical findings at the RAM, for which 6 NACs were excised and 9 NACs were preserved. Three excised NACs showed benign histology and were excised for findings at the RAM of IDC, DCIS, and ADH. The 3 other excised NACs were for DCIS with pagetoid spread along the nipple ducts at RAM and contained DCIS in the excised NACs. With a median follow up period of 703 days (range 123–2071) for all patients and 708 days (range 123–1845) for patients with preserved NACs, there were no instances of NAC recurrence. There were 2 cases that had both non-NAC LR (2.7%) and distant metastases (2.7%). Both cases had excision of the NAC showing benign histology, excised for DCIS and ADH at the RAM. The former case represents the only patient in this series who was reported as deceased.

3.2. Analysis of positive and atypical diagnoses

Table 2 provides individual case details and length of follow up on the 15 cases (20.3%) with positive or atypical findings of the RAM by FS or permanent histology. Overall, there were 7 positive RAMs (9.5%) on permanent histology, of which 6 (85.7%) were DCIS and 1 (14.3%) was IDC. The RAMs also showed 1 LCIS (1.4%), 4 ADH (5.4%), and 2 UDH (2.7%) by permanent histology. All 4 positive diagnoses by FS (1 IDC and 3 DCIS) were confirmed on the permanent histology slide. Two cases of DCIS underwent additional shave biopsy of the subareolar tissue, which demonstrated benign histology in one and DCIS in the other, both concordant on FS and permanent histology. Only 1 of the 3 NACs excised subsequent to a positive RAM on FS demonstrated malignant histology (DCIS, pagetoid spread).

A single case of LCIS at the RAM, demonstrated by 2 confirmed

Table 2
Positive or atypical/proliferative diagnoses of the retroareolar margin.

Case	Intraoperative diagnosis	Permanent diagnosis	Additional margin diagnosis[a]	Nipple-areolar complex diagnosis	Follow up (days)
1	IDC	IDC	N/A	Negative	411
2	DCIS	DCIS	DCIS	DCIS, pagetoid	506
3	DCIS	DCIS	N/A	UDH	755
4	DCIS	DCIS	Negative	N/A	308
5	LCIS	LCIS	LCIS	N/A	503
6	ADH	DCIS	N/A	N/A	492
7	ADH	DCIS, pagetoid	N/A	DCIS, pagetoid	464
8	Negative	DCIS, pagetoid	N/A	DCIS, pagetoid	542
9	Negative	ADH	N/A	Negative	1461
10	Negative	ADH	N/A	N/A	316
11	Negative	ADH	N/A	N/A	802
12	ADH	ADH	N/A	N/A	377
13	ADH	UDH	Negative	N/A	1077
14	ADH	UDH	N/A	N/A	741
15	ADH	Negative	N/A	N/A	856

Abbreviations: ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; LCIS, lobular carcinoma in situ; UDH, usual ductal hyperplasia; N/A, not applicable.

[a] Additional shave of retroareolar tissue taken following initial intraoperative diagnosis.

Table 3
Diagnoses of the retroareolar margin, intraoperative evaluation compared to permanent histology.

Retroareolar margin	Permanent histology		
	Positive[a]	Negative	Total
Intraoperative positive[a]	4	0	4
Intraoperative negative	4	70	74
Total	8	70	78

[a] Invasive disease and/or ductal carcinoma in situ.

sequential FS, showed no evidence of disease at 503 days of follow up. Two RAMs with ADH and 1 negative RAM by FS showed DCIS on permanent histology slide, and 2 of 3 excised NACs were positive for DCIS with pagetoid spread, corresponding to the RAM findings. The preserved NAC with DCIS at the RAM showed no evidence of disease at 492 days of follow up. Four cases with ADH of the RAM diagnosed on permanent histology (3 negative and 1 ADH by FS), showed no evidence of disease at 316, 377, and 802 days of follow up for the 3 preserved NAC, and benign histology for the 1 excised NAC. This case represents the only NAC excised due to an atypical lesion. A separate case was identified as ADH by FS of the RAM (UDH by permanent histology) but was not excised due to a negative secondary subareolar shave.

3.3. Diagnostic accuracy and multivariable analysis

The concordance and discordance between FS and permanent section diagnosis of RAM is reviewed (see Table 3, Fig. 2). There were 4 false negative cases and no false positive cases. Intraoperative evaluation of the RAM showed 50% sensitivity (95% CI 17.4–82.6), 100% specificity (95% CI 93.5–100), 100% PPV, 95% NPV, and 95% concordance rate. When re-reviewing the 4 false negative cases, it is noted that technical causes including superficial sectioning (tumor only present on deeper permanent sections), tissue folding, and suboptimal staining were the main reasons of discrepancy.

Table 4 demonstrates the results of univariate analysis of selected variables compared by RAM status. The subpopulation totals for positive RAM alone or for positive NAC diagnoses were both too small in quantity for meaningful statistical analyses. Gross measurement of the tumor to nipple distance in the mastectomy specimens was the only parameter identified to have statistical significance in association with a positive RAM. This finding was verified by multivariable logistic regression with an odds ratio of 0.475 (95% CI: 0.238–0.946) after adjusting for age, length of follow up, preoperative radiologic measurement of FTN, largest tumor size, tumor focality, neoadjuvant chemotherapy, and presence of DCIS.

4. Discussion

Although the benefits and oncologic safety of NSM have been well-established, clinical practice including the evaluation of the RAM and management of atypical epithelial proliferative lesions identified on RAM are variable among institutions. This study aims to help define our institutional practices and outcomes, and further clarify the role of FS of the RAM in patient management, particularly for atypical epithelial proliferative lesions.

Early studies show a wide range of 5.6–58% carcinoma involvement of the NAC, which reflects the heterogeneity of the inclusion criteria and study protocols [22-26]. More recently, *Brachtel* et al. demonstrated occult involvement of the NAC in 21% of therapeutic mastectomies [27]. The majority of NAC involvement was by direct extension of DCIS. Our study population included 3 NACs involved by DCIS with pagetoid spread, representing 4% of therapeutic mastectomies. This low level of involvement likely reflects our stringent patient selection criteria and precludes significant statistical analysis for predictive factors. However, it supports pagetoid spread as a strong predictor for NAC involvement, which should be included in the diagnostic evaluation of subareolar nipple ducts to guide surgical management.

Several additional risk factors for NAC involvement have been proffered, including Her2 enrichment, tumor size, and FTN [27,28]. Radiologic evaluation has been shown to be moderately predictive of RAM positivity, but with only a marginal increase in sensitivity when added to pathologic FS [29,30]. Only two cases in our study had a preoperative FTN less than 2 cm, but radiologically occult tumor involvement closer than 2 cm FTN was identified in 12 cases, which were predominantly DCIS. Univariate analysis and multivariable logistic regression isolated postoperative gross measurement of FTN in surgical pathology as the only factor significantly associated with a positive or atypical diagnosis of the RAM (adjusted odds ratio 0.475, 95% CI: 0.238–0.946).

Most reviewed study protocols included strict patient selection criteria, and a systematic review of the literature by *Headon* et al. in 2016 concluded that NSMs should be restricted to peripheral tumors more than 2 cm FTN, less than 5 cm in size, and Her2 negative [30]. Alternatively, from 2013 to 2018, 5 studies including 1982 therapeutic NSMs were reported from institutions which had loosened criteria to exclude only those patients with evident nipple or skin involvement, plus or minus marked ptosis and macromastia [13,14,17,18,32]. They collectively report a tumor size range of <0.1–15 cm, FTN range of <0.1–11 cm, RAM positivity rates of 2.7–34.2% (mean: 11%), NAC positivity rates of 1.4–13.1% (mean: 6.2%), and no recurrences in the NAC. In a selection of recent studies with more restrictive criteria, the mean RAM positivity and NAC positivity rates were 10.5% and 8.3%, respectively [5,8,16,19,27,29]. Our study population similarly showed 9.5% positive RAMs and 4.1% positive NACs.

Two common methods of RAM sampling reported in the literature include a thin *en face* margin, as used at our institution, and a thick perpendicularly-section disc [14,17,19,30]. Any tumor present in the *en face* margin is considered positive, whereas varying cutoffs are proposed for perpendicularly-sectioned RAMs. Evaluation is additionally complicated by inconsistent reporting and management of atypia and LCIS as positive or negative [12-19]. Our data shows atypical lesions are routinely treated as negative at our institution, with the exception of an early case in which a single RAM positive for ADH led to subsequent

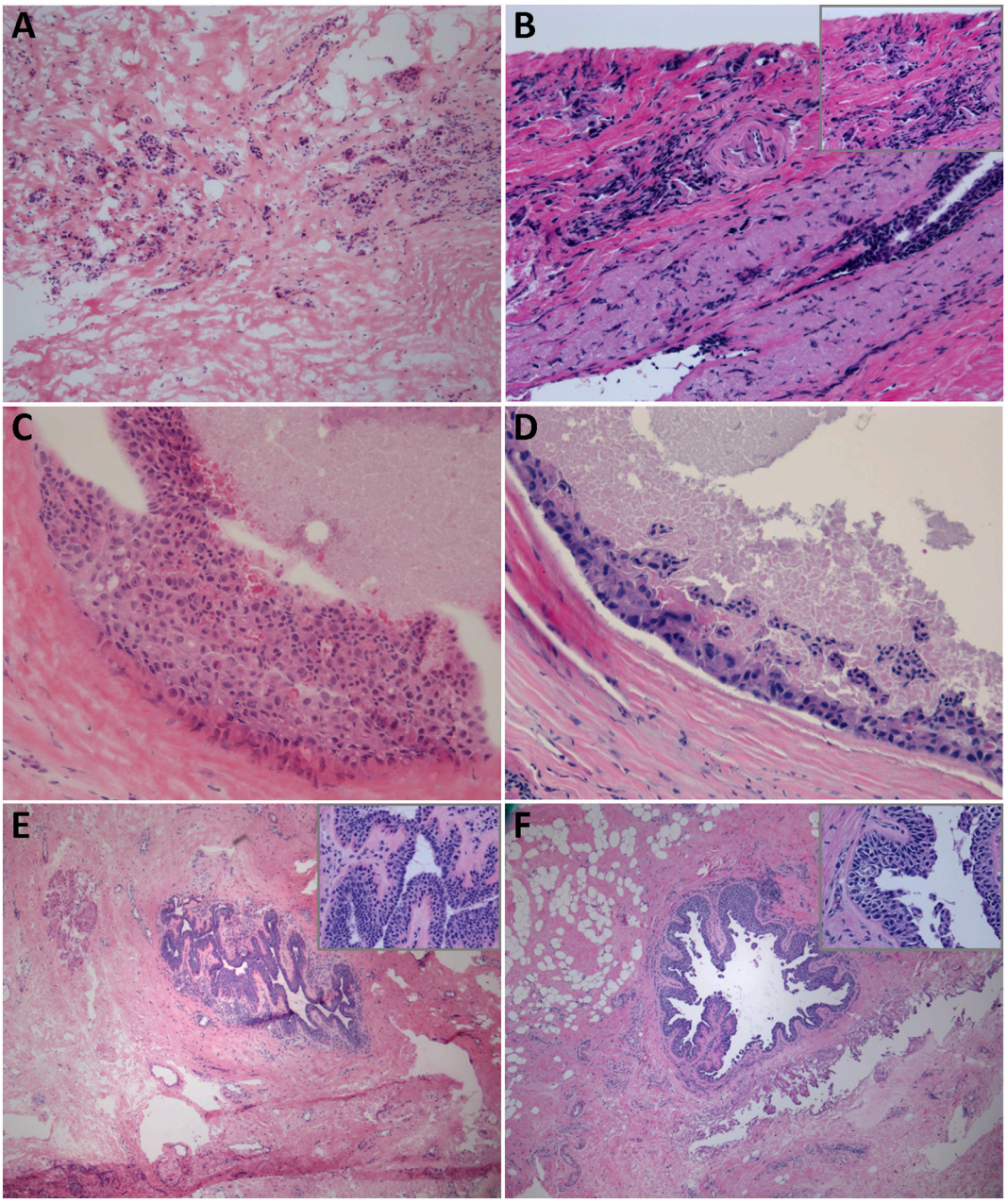

Fig. 2. Correlation between frozen section (FS) and permanent section diagnosis on retroareolar margins. A. Invasive ductal carcinoma on FS (H&E, x40); B. Invasive ductal carcinoma on permanent section (H&E, x100; inset: x200); C. DCIS on FS (H&E, x100); D. DCIS on permanent section (H&E, x200); E. Negative on FS (H&E, x40; inset: x200); F. Positive for pagetoid spread DCIS on permanent section (H&E, x100, inset: x200).

excision of a benign NAC.

The diagnostic accuracy of FS in evaluating RAM has been assessed in a limited number of recent single-center studies [14,15,18,19]. They report ranges for sensitivity, specificity, PPV, and NPV of 58–88.4%, 88–100%, 70–88.4%, and 91.7–94%, respectively. Reflecting our conservative diagnoses of atypia in cases determined to represent true DCIS on permanent histology, we report 50% sensitivity, 100% specificity, 100% PPV, and 95% NPV. The overall concordance rate of 95% in our study also exceeds the reported range of 85.3–92.1%. The majority of reported studies do not exclude prophylactic NSMs and specimens with no residual disease, which artificially inflate accuracy figures with a large number of true negatives. False positive and false negative rates have been reported at 0–11.5% and 5.9–9.3%, respectively [14,15,18,19,33]. We report a 5.1% false negative rate and no false positives.

Management of margins positive for DCIS or invasive disease includes observation only, additional retroareolar sampling, intraoperative radiation, postoperative radiation, nipple-only excision, and NAC excision. Choice of NAC management depends on patient preference, tumor pathology, surgeon experience and available resources. Our institution does not utilize intraoperative radiation, and PMRT was used in 10.8% of cases, all for indications irrespective of RAM status. Although it has been shown that PMRT increases the risk of nipple necrosis, none of the patients in our study who received PMRT experienced nipple necrosis [34]. Our overall rate of nipple necrosis or inadequate nipple perfusion was 2.7%, compared to a reported 5.9% average [31].

Excision of the NAC, additional retroareolar sampling and observation are the most common forms of management in our institution. We had one case of DCIS at the RAM with an additional intraoperative section of the RAM showing benign histology. The NAC was preserved

Table 4
Univariate analysis by retroareaolar margin status.

Characteristic	Mean by RAM status		
	Positive/ Atypical	Negative	*p*-value
Age (years)	49	49	0.8969
Largest tumor focus (cm)	1.5	1.6	0.6502
Closest tumor to nipple-areolar complex			
Radiologic preoperative measure (cm)	3.6	4.5	0.1802
Pathologic postoperative measure (cm)	2.5	3.9	0.0307[a]
Length of follow up (days)	641	777	0.2326
Tumor focality	2.0	1.5	0.2011

Abbreviations: RAM, retroareolar margin.
[a] Significant by multivariable analysis, adjusted odds ratio 0.475 (95% CI 0.238–0.946).

and showed no evidence of disease at 308 days follow up. Based on patient preference, a single case of DCIS at the RAM did not receive additional excision of the RAM or NAC excision with no evidence of disease at 492 days follow up. This case did not demonstrate pagetoid spread. Five recent reports include 31 instances of preserved NACs overlying RAMs positive for DCIS or invasive disease and no evidence of NAC recurrence with a weighted 31 month mean follow up period (see Table 5) [12-15,17,19]. Although the number is not specified in each study, at least 6 of these cases received PMRT.

Our study population also included preserved NACs with RAMs positive for LCIS and ADH with no evidence of NAC recurrence at 500 days mean follow up. A limited number of reports detail management and outcome of atypia and precursor lesions at the RAM [15,17,19]. These include 48 instances of preserved and untreated NACs with RAMs positive for atypia (83% LCIS, otherwise unspecified) and no evidence of NAC recurrence with a weighted 33 month mean follow up (see Table 5). As demonstrated in our case series, the definitive designation of atypical epithelial proliferative lesions must be confirmed by permanent histology to avoid undertreatment and overtreatment of false negative and false positive results, respectively.

In accordance with the preponderance of evidence, our institution utilizes FS of the RAM in NSMs with high pathologic concordance and NPV in a carefully selected patient population. While still investigational, favorable reports of less strict patient selection criteria and conservative management of RAMs are growing. Patients with false negative FS of the RAM may have the NAC excised at subsequent reconstruction and revision, or as a separate procedure not requiring general anesthesia. However, appropriate NAC excision at the time of NSM allows for single-stage reconstruction and improves reconstructive planning. In addition to potentially reducing the number of overall surgeries for patients, FS can reduce patient anxiety and help to establish expectations for surgical outcome. To this end, accurate FS relies on intentional interdisciplinary communication and experienced pathology technical staff to produce high-quality FS histology.

5. Conclusions

Nipple-sparing mastectomy is an oncologically safe procedure with preferable cosmetic and psychological outcomes. There is significant heterogeneity in patient selection, surgical technique, pathology protocols, and management of positive RAMs. Intraoperative frozen section evaluation demonstrates high concordance with permanent histology, moderate sensitivity, high negative predictive value and no false positive diagnoses in our study. Negative RAMs, including diagnoses of atypical epithelial lesions, can safely lead to preservation of the NAC, as it has shown no increased risk of recurrence in our study. Less conservative patient selection criteria and preservation of NACs overlying DCIS and invasive carcinoma may also prove a viable option upon extended follow up. Although positive RAM alone does not accurately predict NAC involvement, pagetoid spread along the nipple ducts appears to be a strong predictor for NAC positivity.

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Declaration of competing interest

None.

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Table 5
Reports of positive/atypical retroareolar margins with preserved nipple-areolar complexes.

Study	Mean follow up (months)	Number of preserved NACs by RAM lesion					
		Invasive	DCIS	LCIS	ADH	Atypia[a]	Total
Haslinger et al. [12]	38.4		5				5
Amara et al. [13]	31.3	6	7				13
D'Alonzo et al. [14]	36		2				2
Suarez-Zamora et al. [15]	16.5					2	2
Tang et al. [17]	36	2	5	36		6	49
Eisenberg et al. [19]	10		4	4			8
This study	16.6		1	1	3		5
Total		8	24	41	3	8	84

Abbreviations: NAC, nipple-areolar complex; RAM, retroareolar margin; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ADH, atypical ductal hyperplasia.
[a] Unspecified atypia without formal diagnosis.

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