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Accuracy and interobserver agreement of retroareolar frozen sections in nipple-sparing mastectomies

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ABSTRACT

In the last decades, surgical treatment of breast cancer has enormously changed. As a result, nipple-sparing mastectomy (NSM) has evolved as an oncologically safe and cosmetic approach. NSM includes a subareolar frozen section to evaluate malignancy. We determined the accuracy of subareolar frozen section diagnosis, analyzed the discrepancy factor, and estimated the interobserver agreement of frozen section in NSM. A retrospective review of all NSMs at our institution from 2009 to 2015 was performed. Frozen sections were compared to the final diagnoses to analyze the accuracy of subareolar frozen sections. Discordant results were rigorously evaluated to identify discrepancy factors. Some cases were randomly chosen to assess the interobserver agreement (*kappa*) among pathologists. The agreement results were evaluated with and without knowledge of the tumor morphology. Among 34 NSMs, the frozen section false-negative and false-positive rate was 5.9% and 8.8%, respectively. The sensitivity and specificity was 77.8% and 88.0%, respectively. Sampling errors and diathermy artifacts explained our false-negative diagnoses. Freezing artifacts and an intraductal papilloma explained our false-positive diagnoses. The interobserver agreement between breast and general pathologists was 0.87 ($p < 0.0001$) and 0.31 ($p = 0.0001$), respectively. The interobserver agreement increased to 0.35 ($p < 0.0001$) in general pathologists with knowledge of the tumor morphology. Subareolar frozen section showed to be a specific test with moderate sensitivity. Papillary lesions can mimic atypical cells and influence the frozen section interpretation. Frozen section in NSM had a better performance in breast pathologists (almost perfect) versus general pathologists (fair). Interobserver agreement may improve with knowledge of tumor morphology.

1. Introduction

Breast cancer is the most common cancer in women and a major public health concern worldwide [1]. It is estimated that 1.8 million new cases of breast cancer were diagnosed in 2013 with about 464,000 related deaths around the world [2]. Significant progress has been made in the surgical management of this cancer during the last decades. As a result, the use of nipple-sparing mastectomy (NSM) has significantly increased due to the interest in a more conservative approach and a better cosmetic result [3]. During this surgical procedure, all the breast parenchyma with the tumor is removed, but the skin and the nipple-areola complex (NAC) are preserved [4].

There are several benefits related with NAC preservation, including reduction of the perception of mutilation, higher psychological benefits among women [3], and local recurrence rates statistically similar to other types of mastectomies in well-selected candidates (11.7% in NSM, 10.4% in skin-sparing mastectomy, and 11.5% in modified radical mastectomy) [5,6]. NSM usually includes an intraoperative frozen section of the retroareolar tissue to evaluate the presence of occult malignancy and to decide if NAC will be preserved or resected according to histological findings [7]. Although there is no clear consensus regarding NAC preservation, the nipple is frequently removed if malignant cells are found on either frozen on permanent sections. If the NAC has tumor cells on frozen section, it is frequently excised during the mastectomy, but if the frozen section is negative for malignancy and the final diagnosis is positive for carcinoma, the NAC

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Table 1
Subareolar frozen section and final histopathology reports for 34 nipple-sparing mastectomies.

	Positive permanent	Negative permanent	Total
Positive frozen	7	3	10
Negative frozen	2	22	24
Total	9	25	34

should be removed in a separate surgical procedure or during a second stage of breast reconstruction [8].

The primary aim of this study was to investigate the accuracy of retroareolar frozen section interpretation, to analyze the reason for discrepancy between frozen section diagnosis and permanent section diagnosis, and to determine the interobserver agreement of subareolar frozen section in NSM.

2. Materials and methods

After obtaining the institutional ethics committee approval, a retrospective review of our pathology database was conducted to identify all the patients who had NSM and intraoperative subareolar frozen section from 2009 to 2015 at our institution. We included NSMs performed for both prophylactic and therapeutic purposes. Demographic, operative, and pathologic information was collected from the electronic medical record.

Frozen section diagnosis was compared to the final diagnosis given on permanent sections in order to analyze the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of subareolar frozen section interpretations. Discordant results were meticulously evaluated to determine the reasons for the discrepancies. To assess interobserver agreement, 15 cases were randomly chosen. Two pathologists with breast interest and four general pathologists from our institution retrospectively evaluated the retroareolar frozen section slides. Each pathologist had a maximum time of 5 min per slide to make his or her diagnosis without knowing the morphology of the primary tumor. No consultation was allowed for the purpose of this study. The frozen section diagnosis given by each pathologist was categorized into “positive for carcinoma”, “negative for carcinoma”, or “atypical” if the findings on the frozen section slide were worrisome but not sufficient to diagnose carcinoma. Finally, all frozen section slides were re-interpreted by each pathologist with knowledge of tumor morphology.

For the purpose of statistical analysis, “positive” cases and “atypical” cases were lumped together and treated as “positive”. *Kappa* statistics were applied to measure the degree of interobserver agreement between breast and general pathologists. The degree of agreement was interpreted as follows: slight agreement (k = 0.00–0.20), fair agreement (k = 0.21–0.40), moderate agreement (k = 0.41–0.60), substantial agreement (k = 0.61–0.80), and almost perfect agreement ($k \geq 0.81$). All statistical analyses were performed using STATA^{R} (version 14.0, StataCorp LP, College Station, Texas, USA). Statistical significance for all analyses was defined as $p < 0.005$.

3. Results

Between 2009 and 2015, 34 NSMs with subareolar intraoperative frozen sections were performed at our institution. Of these, 30 (88.2%) were performed for therapeutic indications, three (8.9%) for high-risk prophylactic resection, and one (2.9%) for contralateral prophylactic resection. The age of the patients ranged from 34 to 68 years with a mean age of 46.5 ± 10.5 years, and all were women.

3.1. Accuracy of subareolar frozen section

Among 34 NSMs, 70.6% (n = 24) of subareolar frozen sections were classified as negative for carcinoma, 14.7% (n = 5) were classified as atypical cells, and 14.7% (n = 5) were classified as positive for carcinoma. On permanent pathology, 73.5% (n = 25) of frozen section controls were considered negative for carcinoma and 26.5% (n = 9) were considered positive for carcinoma (Table 1). Therefore, the frozen section false-negative and false-positive rate was 5.9% (n = 2) and 8.8% (n = 3), respectively. The sensitivity, specificity, PPV, NPV, and accuracy of subareolar frozen section diagnosis in our institution was 77.8%, 88.0%, 70.0%, 91.7% and 85.3%, respectively.

Of the five positive subareolar frozen sections, all (100%) nipples were resected during the mastectomy. Of the five atypical subareolar frozen sections, two (40%) nipples were resected during the mastectomy, one (20%) was preserved intraoperatively but was resected in a secondary procedure months later due to local recurrence, and two (40%) were never resected (Table 2).

3.2. Analysis of discordant cases

Discrepancy between the frozen section and the final diagnosis was found in 5 cases and are summarized in Table 3. The first false-negative frozen section was caused by sampling error and a carcinoma in situ was found only on deeper sections of the frozen section control (Fig. 1). The second one was an interpretation error produced by severe diathermy artifacts (Fig. 2). On the other hand, the first false-positive frozen section was due to artifacts created by the freezing process. The slides of the second one were not available for review and we could not analyze the reasons for discrepancy. Finally, the third one was interpreted as atypical cells and the nipple was resected intraoperatively, but deeper permanent sections revealed an intraductal papillary lesion (Fig. 3). Clinical follow-up information was available for all discordant cases. None of these patients experienced local recurrence or metastasis with a median follow-up of 19.4 months.

3.3. Interobserver agreement

The agreement results without knowledge of the primary tumor are summarized in the Table 4. All pathologists had complete agreement in only 7 (46.7%) cases without knowledge of the primary tumor. Breast and general pathologists had 93.3% (14/15) and 46.7% (7/15) of concordant cases, respectively. The interobserver agreement (*kappa* value) among two breast pathologists and four general pathologists was 0.87 ($p < 0.0001$) and 0.31 ($p = 0.0001$), respectively.

Table 2
Management of atypical subareolar frozen section cases.

Frozen section	Intraoperative NAC resection	Permanent section	Second-stage NAC resection	Local recurrence, follow-up	Metastasis
Atypical cells	Yes	Positive for CIS	Resected intraoperatively	NA	NA
Atypical cells	Yes	Negative	Resected intraoperatively	No, 20 months	No
Atypical cells	No	Atypical cells, terminal ducts with IC	Yes, it was positive for CIS and IC	Yes, 12 months after mastectomy	Yes, liver
Atypical cells	No	Negative	No	No, 19 months	No
Atypical cells	No	Negative	No	No, 14 months	No

NAC: nipple-areola complex; CIS: carcinoma in situ; IC: invasive carcinoma; NA: not available.