

## The Accuracy of Intraoperative Subareolar Frozen Section in Nipple-Sparing Mastectomies

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### ABSTRACT

**Background:** Intraoperative subareolar frozen sections are used to assess the nipple areolar complex's suitability for preservation for patients selected for nipple-sparing mastectomy. We aim to investigate the accuracy and value of the frozen section compared to formal histopathologic results.

**Methods:** In our 5-year retrospective study, 52 candidates for nipple-sparing mastectomies had subareolar frozen sections analyzed intraoperatively for malignant or atypical duct changes. Women were considered for nipple-sparing mastectomy if their primary breast malignancy was greater than 3 cm from the nipple-areolar complex and not multifocal in nature. Frozen-section results were compared to the formal histopathologic results, allowing analysis of the sensitivity, specificity, and predictive value. Causes of false negatives (negative frozen-section findings, positive histopathology findings) were then examined.

**Results:** Of 52 frozen sections, 47 (90%) yielded negative results and 5 (10%) yielded positive results. Of the 47 negative results, 39 were true negatives while 8 were false negatives. Of the 5 positive results, all were true positives with no false positives. Therefore, the positive predictive value of subareolar frozen section is 100%, negative predictive value 83%, sensitivity 38%, and specificity 100%. Of the 8 false negatives, 4 (50%) were due to sampling

errors, 3 (37.5%) were due to interpretation errors, and 1 (12.5%) was due to diathermy artifact.

**Conclusion:** Intraoperative subareolar frozen section is a specific but nonsensitive test. It is useful in nipple-sparing mastectomy because in 10% of cases a positive result allows immediate nipple and areolar excision. Its low sensitivity and negative predictive value means that 15% of patients will need a subsequent nipple and areolar excision. Eighty-five percent of patients can, however, have a single-stage excision.

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### INTRODUCTION

With the advent of breast screening, genetic screening, and community education, breast cancer is being detected earlier, and prophylactic mastectomies are becoming more common. The treatment of breast cancer has evolved, with treatment options including skin-sparing and nipple-sparing mastectomy. The cosmetic benefits of skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) with immediate breast reconstruction need to be weighed against its oncologic safety.<sup>1</sup>

The difference between SSM and modified radical mastectomy (non-skin-sparing mastectomy) is the skin envelope preservation in the former, with the same amount of breast tissue. SSM also entails excision of any biopsy scar, skin obviously involved by tumor, or overlying superficial tumor in order to reduce the risk of local recurrence.<sup>2</sup>

The conventional SSM involves excision of the nipple and areolar complex (NAC). This can have a significant impact on the overall cosmetic result of the breast reconstruction.<sup>2</sup> The NAC is removed because of the belief that the NAC and its adjacent ducts may harbor tumor cells that have spread distally along the ducts from the primary tumor. Involvement of the NAC

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with breast cancer has been the subject of multiple studies, with differing results.

Cense et al<sup>3</sup> found that the reported rate of NAC involvement with tumor varies from 5.6% to 58%. However, if we limit the review of Cense and colleagues to those studies in which more than 200 mastectomy specimens were analyzed, the rate of NAC involvement with tumor varies from 5.6% to 23.4%. This variation may be due to the different exclusion criteria of the studies. For example, Laronga et al<sup>4</sup> excluded prophylactic mastectomy, lobular carcinoma in situ, and patients with clinical nipple involvement. The NAC was found to be involved in 5.6% of the cases. Wertheim and Ozzello,<sup>5</sup> on the other hand, did not have any exclusion criteria and found that the NAC was involved in 23.4% of cases.

Various authors have suggested risk factors to help predict NAC involvement with tumor. Risk factors include lymph node involvement, tumor-nipple distance, multicentricity, tumor size, and grade.<sup>3,4,6</sup>

The oncologic safety of NSM and SSM compared to modified radical mastectomy is debated. To date, there are no randomized controlled trials comparing the oncologic safety in these 3 groups. There is a concern that leaving behind the nipple or skin may increase the rate of local recurrence, metastatic rate, and breast cancer deaths. Gerber et al, however, showed that there is no statistical difference in these 3 endpoints in all 3 groups of patients during a mean follow-up period of 101 months.<sup>7</sup> In this study, 246 selected patients with an indication for a modified radical mastectomy, no skin involvement, and tumor margins greater than 2 cm from the nipple were treated with either NSM, SSM, or modified radical mastectomy.<sup>7</sup> An NSM was performed only if intraoperative subareolar frozen section was negative for tumor.<sup>7</sup> The results of this study are consistent with other studies and reviews of this topic.<sup>7-9</sup>

Leaving the skin behind with an SSM can contribute to a better esthetic result in multiple ways (as compared to a modified radical mastectomy). First, the skin left behind with an SSM is of a better color and contour match than the skin paddle of any flap used for reconstruction. Second, the incision used often results in a shorter and less prominent scar than that of a modified radical mastectomy. Third, with the use of tissue expander reconstructions, by having more skin left behind, the remaining skin does not need to be stretched as much or sometimes not at all to reconstruct the new breast. This avoids the thinning of the dermis, associated with tissue expansion, which may contribute to a more esthetically pleasing appearance. Fourth, the entire skin paddle of the flap used for reconstruction will be tattooed to recreate the nipple. This helps to hide the scar and make the flap edges less obvious. Finally,

preservation of the skin gives the reconstructive surgeon the option of immediate reconstruction with an implant rather than with a tissue expander.

Preserving the nipple-areolar complex can further enhance the esthetic appearance in a number of ways.<sup>10</sup> The nipple is an important esthetic unit, with symbolic and psychologic significance. Its loss may be as or more psychologically significant than the loss of the breast mound itself. The reconstructed nipple will not have the same psychologic benefits as the original. Also, from a technical point of view, it is often not possible to recreate a nipple of the correct shape, volume, projection, color, and texture as the original. Despite multiple techniques being available for nipple reconstruction, the results of these techniques are inconsistent and rarely achieve as natural an appearance as the native nipple.

NSM and SSM also have disadvantages when compared with the modified radical mastectomy. First, with NSM, there is still some breast tissue left behind, with the potential for malignant changes. Second, an incomplete excision with tumor left behind on the base of the nipple means that another operation will be required for nipple excision. The nipple excision at this later stage can impact negatively on the cosmetic appearance and potentially cause a skin shortage, which could have otherwise been corrected if the nipple had been initially excised and a flap with a bigger skin paddle harvested. Third, an SSM and NSM is technically more challenging and can be complicated by skin and/or nipple necrosis. The rate of nipple necrosis with NSM was estimated by Sacchini<sup>11</sup> to be about 11%.

Our practice is to offer selected patients the option of nipple- and areola-sparing mastectomy in conjunction with immediate breast reconstruction. Patients are considered for NSM if their primary breast malignancy is more than 3 cm from the NAC and not multifocal in nature.

While tumor size, distance of the tumor from the NAC, and tumor multicentricity can help predict which patients will be more likely to have NAC involvement, it is still difficult to know for certain whether the NAC is infiltrated by cancer preoperatively.<sup>12</sup> Crowe et al<sup>12</sup> suggested that an intraoperative subareolar frozen section (ISFS) should be performed to assess the suitability of NAC preservation. With our approach, the presence of malignant cells or atypical duct cells seen in the ISFS led to an intraoperative decision to excise the NAC.

To date, there are no known published articles considering the accuracy of the ISFS in detecting NAC involvement with malignant or atypical duct cells. This study investigated the positive predictive value, negative predictive value, sensitivity, and specificity of ISFS compared to the formal paraffin histopathologic

**Table 1. Frozen-Section Results as Compared to Histopathologic Results (n=52)<sup>a-d</sup>**

	Histopathology Positive	Histopathology Negative
Frozen-section positive	5	0
Frozen-section negative	8	39

<sup>a</sup> Sensitivity: 5/13 or 38.46%.

<sup>b</sup> Specificity: 39/39 or 100%.

<sup>c</sup> Positive predictive value: 5/5 or 100%.

<sup>d</sup> Negative predictive value: 39/47 or 82.98%.

results. False negatives (ISFS negative, histopathology positive) were further examined to determine why the abnormal cells were not detected on ISFS.

## METHODS

In a 5-year retrospective study, 52 candidates for NSM had ISFS analyzed for malignant or atypical duct changes. Surgery was performed at Mount Hospital, Perth, Western Australia, by 3 breast surgeons, and the frozen sections were analyzed by 7 different histopathologists.

A lateral skin incision was used for the NSM. Intraoperatively, the base of the NAC was first identified. A subareolar biopsy specimen was then obtained and sent for analysis while the NSM and appropriate nodal surgery was being completed. The NAC was always excised if the frozen section showed malignant or abnormal ductal cells. The mastectomy was followed with an immediate reconstruction, either with a free transverse rectus abdominis myocutaneous flap, pedicled latissimus dorsi flap, submuscular tissue expander, or a combination of the latter two. Postoperatively, the formal paraffin histopathologic result was compared to the ISFS result. Patients who had false-negative results (ISFS negative, paraffin-sections positive) required a second operation to excise the NAC.

All frozen sections with a false-negative result were reviewed by a single pathologist to determine why the abnormal cells had not been detected in the ISFS.

## RESULTS

Of 52 ISFSs (Table 1), 47 (90%) yielded negative results and 5 (10%) yielded positive results. Of the 47 negative results, 39 were true negatives while 8 were false negatives. Of the 5 positive results, 5 were true positives and there were no false positives. This makes the positive predictive value 100%, negative predictive value 83%, sensitivity 38%, and specificity 100%.

The rate of false negatives did improve with time (Table 2). However, this was not a significant improvement ( $r = 0.17$ ,  $\beta = -0.103$  and  $P = 0.974$ ).

**Table 2. Rate of False Negatives by Year (n=52)**

Year	No. of cases	No. of False Negatives	Rate of False Negatives, %
1999 (part of)	3	0	0
2000	3	1	33.3
2001	6	1	16.7
2002	15	3	20
2003	16	2	12.5
2004 (part of)	9	1	11.1

Of the 8 false negatives, 4 (50%) were due to sampling errors, 3 (37.5%) were due to interpretation errors, and 1 (12.5%) was due to diathermy artifactual error.

In this study, 25% (13 of 52) of patients had NAC involvement with either malignant or atypical duct cells.

## DISCUSSION

The move toward NSM is not only because of the superior cosmetic result but also because of the low rate of nipple involvement reported and the low rate of local recurrence after NSM.<sup>13</sup> However, a patient's eligibility for NSM should be undertaken in consideration with the tumor type and size, distance to nipple, histologic grade, *HER2* amplification, lymphovascular invasion, and axillary lymph node involvement.<sup>9,13</sup>

This study has shown that ISFS was not a sensitive test for malignancy or duct atypia. A good proportion of patients with negative ISFS results were found to have malignant or atypical duct cells in the formal histopathologic report.

Gerber et al<sup>7</sup> had suggested that false negatives may result even if the subareolar biopsy zone is tumor free because other areas of the NAC not biopsied may contain tumor cells. In our experience, the sampling error tended not to be because only a small fraction of the biopsy sample can be analyzed as frozen sections but rather because the biopsy was sampled from the wrong area. A 3 × 1-cm segment was biopsied, of which only 10% to 15% was analyzed as frozen sections. Thus, even if the frozen section yielded negative results, it did not mean that the biopsy results were negative. Sampling errors accounted for 50% of false negatives.

Preoperative neoadjuvant chemotherapy is common for patients with operable breast cancer. However, the tumor downstaging makes breast-conserving surgery challenging owing to difficulty in preoperative planning and intraoperative macroscopic evaluation of tumor-free margin, and surgeons are often guided by the residual breast mass according to its new margins.<sup>8,9</sup> Loibl et al<sup>8</sup> reported a reexcision rate of 12.4%.

Interpretation errors accounted for 37.5% of false negatives. They included errors due to cancerization of lobules, subtle ductal carcinoma in situ, and mistaking lobular carcinoma for chronic inflammatory changes. Benign duct changes tended to be more common in the subareolar region, making the interpretation of the ISFS more difficult. In this study, the pathologists tended to call the ISFS “negative” unless they were very certain of malignant or abnormal ductal cells. This explains the large number of false negatives as compared to no false positives. A limitation of this study is that 7 different pathologists were involved, which may have led to an increased interpretational error. Interpretation of the pathology results is operator dependant. It is postulated that there is a learning curve in interpreting the histopathology results, and if a single pathologist were to analyze all the specimens, it may improve the predictive value, sensitivity, and specificity of the frozen section. Careful evaluation of retroareolar margin and nipple core tissue will enhance oncologic safety by identifying cases in which NSM is likely to leave residual disease.<sup>10</sup>

Artifactual errors accounted for 12.5% of the false negatives. Artifacts in frozen sections were caused by lipids that did not freeze well. This may reduce the reliability of the analysis. Also, diathermy could cause cellular damage, preventing recognition of cancerous cells.

We believe that the following steps may help to improve the false-negative rate:

1. Analyzing more segments of biopsy specimens rather than just 10% to 15%. This may have time and resource constraints.
2. Having the same histopathologist examine all ISFSs. (In our study, there were 7 histopathologists.)
3. Reducing the use of diathermy when obtaining the biopsy.
4. Adding touch preparation and cytologic smear analysis of the samples.

It was hard to ascertain whether increased experience helped reduce the false-negative rate. In our study, the rate of false negatives did improve with time ( $r = 0.17$ ,  $\beta = -0.103$ , and  $P = 0.974$ ), but this was not a statistically significant improvement. It was accepted that increased experience helped by improving ability to obtain the biopsy and analyze the frozen section.

Being able to do an NSM meant that a better cosmetic result was possible for the 75% of patients without NAC involvement. This rate is comparable to that obtained by Brachtel et al,<sup>13</sup> who found that 79% of patients undergoing mastectomy appeared free of invasive carcinoma or ductal carcinoma in situ; Rusby

et al<sup>9</sup> reported a rate of 75.4%. However, for the 15% of patients who had a false-negative ISFS result, one may argue that they ended up with a worse cosmetic result than if a skin-sparing mastectomy without nipple preservation had been done in the first place. Indeed, if the NAC had been excised initially, a larger skin paddle could have been harvested in the initial reconstruction, to match the contralateral breast. The need to perform a secondary excision resulted in the skin envelope of the affected breast being marginally smaller than the contralateral breast, a result which might be more obvious in smaller breasts. Other drawbacks of a second operation were the increased cost and psychologic trauma to the patient, as well as the risks associated with a second general anesthetic.

## CONCLUSION

The cosmetic benefits of a viable nipple for SSM and NSM with immediate breast reconstruction need to be weighed against its oncologic safety. The intraoperative frozen section is a tool commonly used to help make the decision of whether or not to preserve the nipple. It is thus important to understand the accuracy of this test so that patients can be counseled appropriately. ISFS is a specific but nonsensitive test for detecting malignant or abnormal duct cells. False negatives occurred as a result of sampling, interpretation, and artifactual errors. However, despite the high false-negative rate, ISFS was still useful in NSM: in 10% of cases, a positive result allowed immediate NAC excision. In 75% of cases, the NAC can be preserved. The low sensitivity and negative predictive value of ISFS meant that 15% of patients (with negative ISFS results and positive histopathology results) would need a secondary excision of the NAC. Eighty-five percent of patients can however have a single-stage excision.

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