

Nipple margin assessment at the time of nipple-sparing mastectomy

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Background: Documenting negative margins at the nipple-areolar complex (NAC) during nipple-sparing mastectomy (NSM) remains the standard, but how to achieve this and how to manage a positive margin is debated. We sought to review nipple margin assessments at our institution and to analyze the risk factors of a positive margin and rate of local recurrence.

Methods: Patients who underwent NSM between 2012 and 2018 were reviewed and divided into 3 groups based on indication — cancer, contralateral prophylactic mastectomy (CPM) and bilateral prophylactic mastectomy (BPM).

Results: Nipple-sparing mastectomies were performed on 337 patients; 72% for cancer, 20% for CPMs and 8% for BPMs. Nipple margin assessments were performed in 87.8% of patients; 10 patients (3.4%) had a positive margin, 7 of whom underwent NAC excision and 3 were managed with observation.

Conclusion: As indications for NSM increase, assessment of nipple margin provides valuable information to manage the NAC in patients with cancer. The routine use of nipple margin biopsies in patients undergoing CPM and BPM may no longer be required, as rates of occult malignant disease are low with no positive biopsies. Further studies with larger sample sizes are needed.

Contexte : Il convient toujours de vérifier la présence de marges négatives au niveau de la plaque aréolo-mamelonnaire (PAM) durant la mastectomie avec conservation de la plaque aréolo-mamelonnaire (MCAM), mais on ne s'entend pas sur la façon de le faire et de gérer les marges positives. Nous avons voulu faire le point sur la façon d'examiner les marges au niveau du mamelon et d'analyser les facteurs de risque associés à des marges positives et le taux de récurrences locales à notre établissement.

Méthodes : Les cas de MCAM traités entre 2012 et 2018 ont été passés en revue et divisés en 3 groupes selon l'indication : cancer, mastectomie controlatérale prophylactique (MCP) et mastectomie bilatérale prophylactique (MBP).

Résultats : Des mastectomies avec conservation de la plaque aréolo-mamelonnaire ont été effectuées chez 337 patientes; 72 % pour cancer, 20 % pour MCP et 8 % pour MBP. Un examen des marges au niveau du mamelon a été fait dans 87,8 % des cas; 10 (3,4 %) ont présenté des marges positives, dont 7 ont nécessité une excision de la PAM et 3 ont été maintenus sous observation.

Conclusion : À mesure que les indications de la MCAM augmentent, l'examen des marges au niveau du mamelon fournit des informations utiles pour la prise en charge de la PAM dans les cas de cancer. Une biopsie systématique des marges au niveau du mamelon pourrait ne plus être requise dans les cas de MCP et de MBP, puisque les taux de maladie maligne occulte sont bas en l'absence de biopsies positives. Il faudra procéder à d'autres études sur des échantillons plus volumineux.

Nipple-sparing mastectomy (NSM) represents a paradigm shift in the surgical management of breast cancer. It involves conserving the skin envelope and the nipple-areolar complex (NAC) for enhanced reconstructive outcomes and patient satisfaction.¹⁻³ The usual indications for NSM include prophylactic surgery and early, biologically favourable cancer that is at least 2 cm from the nipple without nipple involvement on imaging or nipple discharge.⁴⁻¹³ Retention of the NAC poses a potential and theoretical threat to the oncological outcomes from this surgery. Locoregional

recurrence after NSM is reported to be 0%–11.7%, and recurrence in the NAC itself is reported at 0%–5%.² For this reason, nipple margin assessments are often performed at the time of NSM. A wide range of positive nipple margin rates (from 0% to 58%) and the risks associated with this margin being positive are poorly understood.^{2,10–17} Management of a positive nipple margin ranges from excision of the NAC, subareolar shave biopsy or observation.¹⁸ With broadening indications for NSM including larger cancers and wider areas of ductal carcinoma in situ (DCIS) compared with only small remote cancers or prophylactic mastectomy historically, nipple margin assessment may be beneficial.

We sought to review the rates of nipple margin assessments performed at the time of NSM at our institution, how the nipple margin was determined, the rate of cancer identified from those margins and how a positive margin was managed. We analyzed the risk factors of a positive margin as well as the rate of local recurrence in our study population.

METHODS

We conducted a retrospective review of a prospectively maintained breast surgery database at Providence Breast Centre. This study was approved by the Research Ethics Board at the University of British Columbia (H18–01022) and by Providence Health Care. All patients who underwent NSM between Jan. 1, 2012, and Dec. 31, 2018, were included. Three groups of patients were identified based on indication for NSM — breast cancer (invasive or DCIS), contralateral prophylactic mastectomy (CPM) and bilateral prophylactic mastectomy (BPM) for risk reduction. Each mastectomy was recorded as an individual event in patients who had bilateral malignant disease, unilateral malignant disease with a CPM or BPM for risk reduction. We collected information including patient demographic characteristics, clinical and radiological characteristics, breast pathology, performance and result of nipple margin assessment and reoperation based on positive nipple margin. The presence of occult malignant disease was recorded for the prophylactic mastectomies. All surgeries were performed by a Providence Health Care breast surgeon, in combination with a plastic reconstructive surgeon.

Statistical analysis

All statistical analyses were performed using Stata 17.0. Demographic and clinical baseline characteristics are summarized and listed using descriptive statistics. Quantitative data are reported as means and follow-up data as medians. Categorical data are presented as frequencies. We used analysis of variance to test for differences among the 3 groups when appropriate.

RESULTS

From 2012 to 2018, 337 NSMs were performed by a Providence Health Care surgeon with 242 (72%) performed for breast cancer, 69 (20%) for CPM and 26 (8%) for BPM for risk reduction (Table 1). All patients were female, with an average age of 51 years. When reviewing patients who underwent NSM for cancer, 41 (17%) had DCIS and 201 (83%) had invasive cancer. Six of the 69 patients (8.7%) who underwent CPM were found to have an occult malignant disease (5 DCIS and 1 invasive cancer). Among the 26 patients who underwent BPM, 1 patient was found to have occult DCIS. Three patients who received CPM underwent sentinel lymph node biopsies owing to preoperative imaging findings of suspicious nodes. Thirty-five patients with cancer did not have an axillary staging procedure because their NSM was a completion mastectomy after initial breast conserving surgery with axillary staging.

Nipple margin assessments were performed in 87.8% of patients who underwent an NSM (296 of 337). All nipple margin assessments were performed by pathological assessment of a separate tissue specimen labelled as nipple biopsy. This may have been a shave margin under NAC or coring of the nipple. Surgical nipple margin assessments occurred in 222 of 242 (91.7%) patients with cancer, 57 of 69 (82.6%) in the CPM group and 17 of 26 (65.4%) in the BPM group ($p < 0.001$). Among these 296 patients, only 10 (3.4%) had a positive margin (Table 2), and they were all patients with cancer. In patients who underwent CPM and BPM, there were no positive margins ($p = 0.18$). Twenty patients with cancer did not undergo nipple margin assessments owing to surgeon preference and patient factors. The current practice is to mark all breast specimens; thus, every patient has the nipple margin marked on the mastectomy specimen. As such, some surgeons would choose to not take a separate nipple margin specimen, for example, if the tumour is very far from the NAC.

We conducted a pathological review and multidisciplinary conference review for the 10 patients with a positive nipple margin; 7 of them went on to have their NAC removed. The remaining 3 patients were managed with observation (Table 3) as they had DCIS. Routine breast imaging for surveillance after mastectomy is not performed at our centre. Patients are monitored with a clinical examination for local recurrence every 6 months. The follow-up time is varied for these 3 patients, as they had their surgery in 2014, 2017 and 2018 and all are still being monitored. Table 3 outlines the tumour characteristics of the patients with a positive nipple margin. Most patients (8 of 10) had a positive margin when undergoing upfront surgery; 2 had neoadjuvant therapy. All but 3 patients underwent some form of adjuvant therapy. When comparing tumour size on imaging and tumour size on

Table 1. Patient and tumour characteristics

Characteristic	Patients with cancer <i>n</i> = 242	Patients undergoing CPM <i>n</i> = 69	Patients undergoing BPM <i>n</i> = 26
Age, yr, mean	52	51.4	49.7
Female, <i>n</i>	242	69	26
Size of lesion on imaging, mm,* mean	21.6	7.54	0
Tumour histology			
DCIS, <i>n</i>	41	5	1
Size of DCIS, mm, mean (range)	21.7 (0–85)	4.3 (1–9)	1
Invasive cancer, <i>n</i>	201	1	—
Size of invasive cancer, mm, mean (range)	16.9 (0–57)	1	—
T stage, <i>n</i>			
Tis	41	5	1
T1	106	—	—
T2	44	—	—
T3	3	—	—
T4	—	—	—
Nottingham grade, <i>n</i>			
I	42	5	1
II	84	—	—
III	68	—	—
Axillary procedure, <i>n</i>			
SLNB	185	3	—
ALND	22	—	—
None	35	66	26
Nodal status, <i>n</i>			
Node positive	57/207	—	—
Node negative	150/207	3/3	—
Lymphovascular invasion, <i>n</i>			
Yes	52/242	1/6	—
No	108/242	—	1/1
Invasive tumour subtype, <i>n</i>			
HR+/HER2-	63/201	2/6	—
HR+/HER2+	10/201	1/6	—
HR-/HER2-	13/201	1/6	—
HR-/HER2+	9/201	—	—
Median follow-up, mo	33.7	44.1	—
Neoadjuvant therapy, <i>n</i>			
Yes	31	—	—
No	211	69	26
Adjuvant therapy, <i>n</i>			
Chemotherapy	68	—	—
Radiation therapy	70	—	—
Endocrine therapy	137	—	—

ALND = axillary lymph node dissection; BPM = bilateral prophylactic mastectomy; CPM = contralateral prophylactic mastectomy; DCIS = ductal carcinoma in situ; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; SD = standard deviation; SLNB = sentinel lymph node biopsy.
*Largest size modality of imaging was used among ultrasonography, magnetic resonance imaging and mammogram.

pathology, most tumours treated with upfront surgery rather than neoadjuvant therapy were estimated to be larger on imaging than pathology. Most of these tumours were 2 cm or more away from the NAC, with the exception of 1 patient who was aware that there would be a very high likelihood of positive nipple margin with their tumour being only 8 mm away from the nipple.

Fifteen recurrences were found among the 222 patients with cancer who had nipple margin assessment: 4 local (to the skin, not at the NAC), 4 regional

and 7 distant (Table 4). The mastectomy specimen margins were reviewed, and none of the patients with local recurrence had positive margins on the mastectomy specimen. Five of the 242 mastectomy specimens (2 with DCIS and 3 with invasive ductal carcinoma) had positive margins, 4 at the anterior margin and 1 at the medial margin. None of the patients who had a positive nipple margin had any recurrence. No recurrences were found in patients who underwent CPM and BPM who were found to have an occult malignant disease. The median

follow-up for patients with cancer was 33.7 months, and 44.1 months for the 6 patients who underwent CPM and were found to have an occult malignant disease.

DISCUSSION

Preserving the NAC during NSM poses a potential threat to the oncological safety of this surgery, owing to its lining of ductal cells that theoretically could develop into cancer.² Most surgeons perform some form of nipple margin assessment at the time of NSM to reduce the risk of occult cancer in the NAC.¹⁹ The technique for performing a nipple biopsy varies among institutions, and could affect the incidence of positive margin.¹⁸ These techniques vary from shelling out the inside of the nipple

to taking a small tissue sample in the subareolar plane. Amara and colleagues¹⁸ described inverting the nipple and excising nipple tissue at the dermal junction, and then coring out the inside of the nipple, which was sent as a separate specimen, whereas Haslinger and colleagues²⁰ described excising nipple tissue at the dermal junction without coring the inside of the nipple afterward. Spear and colleagues²¹ described sharply removing a retro-areolar tissue specimen at the point where all of the ducts converge, without coring out the nipple to avoid compromise to the vascular supply (in case additional excision would be required based on the pathology result). Our institution uses 2 techniques for the nipple biopsy: coring out the nipple and subareolar shave.

The number of NSMs performed at our centre has increased over time, and the indications have broadened, including larger invasive cancers (0–57 mm) and wider DCIS (0–85 mm). Coopey and colleagues⁶ have similarly reported expanded patient eligibility for NSM as experience with the surgery evolves. Preserving the NAC has been shown to significantly improve patient satisfaction in terms of emotional well-being, body image and sexual satisfaction.^{1–8,14,15,19,22–26} With the broadening indications for NSM, it is critical to ensure that preservation of the NAC does not compromise the oncological outcomes from this surgery. Among the 337 NSMs performed at our institution between 2012 and 2018, there was consistent use of nipple margin assessment, with

Table 2. Nipple margin assessment outcomes among patients with cancer or undergoing CPM and BPM who underwent nipple sparing mastectomy

Outcome	Patients with cancer <i>n</i> = 242	Patients undergoing CPM <i>n</i> = 69	Patients undergoing BPM <i>n</i> = 26	<i>p</i> value
Nipple margin assessment performed	222/242	57/69	17/26	< 0.001
Positive margin	10/222	—	—	0.18
Surgery based on nipple margin result	7/10	—	—	—

BPM = bilateral prophylactic mastectomy; CPM = contralateral prophylactic mastectomy.

Table 3. Tumour characteristics of patients with a positive nipple margin (*n* = 10)

Patient	Tumour histology	Tumour size on imaging, cm	Tumour size on pathology, cm	Clinical distance to nipple, cm	Radiological distance to nipple, cm	NAT or upfront surgery	Incision for NSM	Management of positive nipple biopsy	Adjuvant therapy
1	DCIS	1.5	3.2	Not palpable	3	Surgery	Inframammary fold	NAC excision	None
2	DCIS	3.8	0*	Unknown	0.8	Surgery	Inframammary fold	Observation	None
3	Invasive cancer	4.0	3.5	Not palpable	5.5	Surgery	Radial	NAC excision	Endocrine
4	Invasive cancer	0.1	1.7	NA†	NA†	Surgery	Inframammary fold	NAC excision	Chemotherapy, RT and endocrine
5	Invasive cancer	1.5	2.2	5	4	Surgery	Inframammary fold	NAC excision	Chemotherapy, RT and endocrine
6	Invasive cancer	7	4.0	5	5	NAT	Inframammary fold	NAC excision	RT and endocrine
7	Invasive cancer	3	1.2	Unknown	6	NAT	Inframammary fold	NAC excision	RT and endocrine
8	Invasive cancer	0.9	1.6	7	7	Surgery	Radial	NAC excision	Endocrine
9	DCIS	9	8.0	2	5	Surgery	Circumareolar with lateral extension	Observation	None
10	DCIS	4.1	4.0	0.5	2	Surgery	Inframammary fold	Observation	Chemotherapy, RT and endocrine

DCIS = ductal carcinoma in situ; NA = not applicable; NAC = nipple-areolar complex; NAT = neoadjuvant therapy; NSM = nipple sparing mastectomy; RT = radiation therapy.

*Multifocal DCIS.

†Patient had a normal mammogram and ultrasonography performed, but had a palpable mass in the axillary tail of left breast, that was excised and revealed invasive lobular cancer with positive margins. The patient had bilateral magnetic resonance imaging (normal), but elected to proceed with NSM.

Table 4. Local, regional and distant recurrences among patients with cancer who had a nipple margin assessment

Recurrence	Patients with cancer who had a nipple margin assessment* n = 222	p value
Local	4	0.54
Regional	4	
Distant	7	

*Nipple margin was negative among all of these patients.

296 patients (87.8%) undergoing a biopsy. Most patients who had CPM and BPM with risk reduction still had nipple margin assessment, even with very low occult malignant disease rates, and the results of these biopsies were negative. Our findings are similar to those of Brachtel and colleagues¹¹ who found no nipple involvement in patients undergoing NSM for risk reduction. Based on this finding, routine nipple margin assessments using a separate portion of tissue in these prophylactic risk reduction cases may not be necessary in this patient population. Marking the nipple base on the mastectomy specimen is likely sufficient to assess the nipple margin in these cases since risk of occult malignant disease is low. This result should be interpreted with caution given the small sample size in our study, and repeating this study with a larger sample size would be prudent.

Despite NSM being performed for more broad indications for breast cancer, positive nipple margins were uncommon in these patients, implying safe patient selection. Only 10 of 222 (4.5%) patients with cancer who had a biopsy had positive margins, and not all of them resulted in NAC excision. For these patients, the radiological distance of the tumour to the nipple, and the tumour size on imaging compared with the final pathology report varied greatly. A multidisciplinary review deemed the risk of recurrence as low for 3 of these 10 patients; thus, they were observed with clinical examination. This differs from the study by Haslinger and colleagues²⁰ who performed a shave biopsy as initial treatment for every patient with a positive nipple margin. However, Petit and colleagues¹⁶ excised only 7 of 63 NACs with positive margins with no recurrences in these patients for 24 months, suggesting that observing some of these patients based on their specific pathology was likely a safe option.²⁰ Amara and colleagues¹⁸ discussed treating patients with positive margins with radiation therapy alone (no excision), although, in their study, patients treated with radiation had other indications for post-mastectomy radiation (such as larger tumour size or involved axillary lymph nodes) and did not undergo adjuvant radiation therapy solely based on their positive margin. Orecchia²⁷ extensively discussed post-operative radiation therapy after NSM, but its role specifically for treating a positive nipple margin is not yet clear. Further studies are needed to investigate the treatment of positive nipple margins with radiation therapy.

Fifteen patients who underwent a nipple margin assessment in our study had a cancer recurrence: 7 distant, 4 regional and 4 local (to the skin). None of these patients had a positive nipple margin. In fact, none of the 10 patients with positive margins have experienced a local recurrence, even those who were managed with clinical observation rather than excision. Similarly, Valero and colleagues²⁸ reported no recurrences at the NAC among their 449 patients, favouring the oncological safety of NSM. Seventy of the 242 (28.9%) patients with cancer in our study underwent adjuvant radiotherapy, which may account for our findings of low local recurrence and no nipple recurrences. Petit and colleagues¹⁶ argued that perhaps they identified no nipple recurrences owing to adjuvant radiotherapy. Given these results, appropriate patient selection for NSM will have low rates of positive nipple margins, a fraction of which can be managed with observation, leading to low rates of NAC excision.¹⁶

Limitations

The limitations of this study include inconsistent technique for nipple margin assessment and nipple core biopsy (coring out the nipple compared with subareolar shave) among our group of surgeons. This study has prompted review by plastic and general surgeons on how we plan to manage the nipple margin assessment in the 3 different groups. Also, our median follow-up of the patients with cancer was fairly short (33.7 mo). It is crucial to monitor these patients' outcomes to ensure long-term safety of NSM with broadening indications. Owing to referral patterns and resource availability in other centres, this study population is from a wide geographic area with breast imaging in many different facilities. Inconsistent reporting of distance between tumour and nipple was seen in those with a positive nipple margin. We did not review the imaging reports to establish the distance between nipple and tumour for patients who had a negative nipple margin.

CONCLUSION

Our institution consistently performs nipple margin assessments in patients undergoing NSM for breast cancer, contralateral prophylaxis and bilateral prophylaxis. Our data suggest that the routine use of nipple margin biopsies in patients undergoing CPM and BPM may no longer be required, as rates of occult malignant disease are low with no positive biopsy results; however, further studies are needed with a larger sample size. As indications for NSM increase, nipple margin assessments may provide valuable information to manage the NAC; however, a positive margin does not mandate excision of the NAC based on multidisciplinary assessment. Consensus is required regarding how best to assess the nipple margin in patients with cancer.

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Competing interests: Elaine McKeivitt received payment or honoraria at University of British Columbia (UBC) and Continuing Medical Education events for speaking on breast cancer topics. She has also held leadership and administrative roles related to breast cancer for UBC, BC Cancer and Providence Health Care. No other competing interests were declared.

Contributors: L. Cadili, C. Dingee, E. McKeivitt and R. Warburton designed the study. L. Cadili, C. Dingee, E. McKeivitt, J. Pao and R. Warburton acquired the data, which L. Cadili, C. Dingee, E. McKeivitt and R. Warburton analyzed. L. Cadili and R. Warburton wrote the article, which A. Bazzarelli, L. Cadili, C. Dingee, E. McKeivitt, J. Pao and R. Warburton reviewed. All authors approved the final version to be published.

Data sharing: Data for this study are available upon request from the corresponding author.

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