Review Article

Nipple-sparing Mastectomy in Breast Cancer: From an Oncologic Safety Perspective

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Abstract

Objective: To evaluate the oncologic safety of nipple-sparing mastectomy (NSM) for breast cancer patients based on current literature.
Data Sources: A comprehensive literature search of Medline, Embase databases was conducted for studies published through March 2014.
Study Selection: Our search criteria included English-language studies that focused on NSM at nipple-areola complex (NAC) involvement, patient selection, and recurrence. Prophylaxis NSM, case series or reports that based on very small population were excluded. In the end, 42 studies concerning NSM and oncological safety were included into the review.
Results: NSM is a surgical procedure that allows the preservation of the skin and NAC in breast cancer patients or in patients with prophylactic mastectomy. However, the oncologic safety and patient selection criteria associated with NSM are still under debate. The incidence of NAC involvement of breast cancer in recent studies ranges from 9.5% to 24.6%, which can be decreased through careful patient selection. Tumour-nipple distance, tumour size, lymph node involvement and molecular characteristics can be evaluated preoperatively by clinical examinations, imaging studies and biopsies to predict the risk of NAC involvement. Currently, there is no available standard protocol for surgical approaches to NSM or pathological examination of NSM specimens. The local recurrence (ranges from 0% to 24%) of NSM is not significantly higher than that of traditional mastectomy in selected patients based on long-term follow-up. The role of radiotherapy in NSM is still controversial and is not universally accepted.
Conclusions: NSM appears to be oncologically safe following careful patient selection and assessment of margins.

Key words: Breast Cancer; Locoreginal Recurrence; Nipple Involvement; Nipple-sparing Mastectomy

Introduction

Despite breast-conserving surgery is widely accepted as the main surgical procedure in treatment modalities, approximately 20–30% breast cancer patients still require or request mastectomy.[1,2] For these patients, breast reconstruction can be performed immediately or delayed until after mastectomy. Almost 90% of women would choose nipple reconstruction after breast reconstruction.[3] This result highlights the importance of the nipple-areola complex (NAC) in the cosmetic outcome.

However, there are problems with reconstructed nipples, including lack of projection, colour mismatch, shape, size, texture and position. In 1962, nipple-sparing mastectomy (NSM) or subcutaneous mastectomy was first described by Freeman.[4] NSM is a surgical procedure that allows the preservation of the skin and NAC in mastectomy. When the NAC was preserved during mastectomy, patients reported improved satisfaction, body image, and psychological adjustment.[5,6]

Since there is limited evidence and no consensus regarding its oncological safety, NSM has been recommended only in carefully selected patients with experienced multidisciplinary teams by National Comprehensive Cancer Network clinical practice guidelines. The prevailing argument is that if the NAC is left in place, there is a chance of leaving either occult tumour or a certain amount of breast tissue that is at risk of developing subsequent cancer. While the incidence of local recurrence (LR) after NSM has been reported to be as high as 24% of cases, recurrence specifically at the nipple areola region has been reported in only 2% of cases.[7-9] Therefore, selection criteria for NSM in breast cancer patients are urgently needed. In clinical practice, appropriate standard for selecting patients with low risk of NAC involvement has not been well established.[10]

In this review, we highlighted oncologic safety of NSM from the following perspectives: Preoperative patient selection, surgical approach/pathology evaluation during operation, and patient outcome.

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Nipple-areola complex involvement in breast cancer

Nipple involvement is the major issue concerning the oncologic safety of NSM. The incidences of nipple involvement were variable, ranging from 9.5% to 24.6% in recent studies.[11-18] We summarized the characteristics and results of recent studies in Table 1. There were several possible explanations for various nipple involvement incidences.

First of all, some studies included clinically involved NAC while others did not. According to Mallon *et al*., who compared occult NAC malignancy with overall NAC malignancy, the incidence of the former was significantly lower.[19] In Wang *et al*.'s study, the overall NAC malignancy rate was 9.5%.[12] However, after excluding 21 cases with clinically abnormal NAC, the NAC involvement rate fell to 7%.

Secondly, studies that included Paget's disease, ductal carcinoma *in situ* and invasive ductal carcinoma (IDC) reported higher NAC involvement rates, since these lesions were the most common types of lesions that involve the NAC.[12,20,21] Some studies also included the presence of lobular carcinoma *in situ* (LCIS) in the nipple as evidence of malignancy involvement. Because LCIS is regarded as a marker of risk rather than a precursor lesion, the reported incidence of nipple involvement was increased. For instance, in studies that included LCIS, the incidence of malignant NAC involvement (30–58%) was significantly higher than average.[20,22]

Finally, the pathological protocol used for NAC evaluation had a major role in determining the incidence of NAC involvement.[16] Variation in methodology existed between studies regarding the depth of sampling from nipple skin, slicing orientation, slice width, and number of sections per block.[19] Above all, the distance from the base of the nipple examined was ill defined, and a low rate of NAC positivity was associated with longer distance. Pathological protocols that did not require serial coronal sections of the nipple also yielded a lower rate of NAC involvement. Furthermore, a review of pathology records alone might not be appropriate for the evaluation of NAC involvement. According to Schecter *et al*.'s study, only 4 of 13 cases of NAC involvement were identified based on a review of medical records alone, the others were identified by the pathologist upon re-examination of the NAC sections from all study patients.[23]

Risk factors for nipple-areola complex involvement and preoperative patient selection

Preoperative patient selection is essential for NSM oncological safety. Careful patient selection could decrease the incidence of NAC involvement, thus decreasing LR rates. Possible factors that should be considered for evaluation before NSM include: clinical evaluations of nipple involvement, tumour-nipple distance (TND), tumour size, axillary lymph node involvement, disease stage, histological grade, human epidermal growth factor receptor-2 (Her-2) overexpression, and hormone receptor status.

Clinical evaluations

Clinical evaluation is the key to select proper NSM candidates. One study showed that clinical NAC involvement, as determined by patient symptoms or physical examination (e.g., nipple retraction, palpable mass in the nipple, nipple bleeding or nipple discharge), was present in 61% of NAC-positive but only 14% of NAC-negative cases.[13] Another study demonstrated that, the sensitivity of detecting NAC involvement was 61% with clinical evaluation (history and/or physical examination) and 56% with magnetic resonance imaging (MRI),[24] indicating the importance of clinical evaluation in preoperative patient selection.

Tumour-nipple distance

Tumour-nipple distance was the most notable factor associated with NAC involvement among all the investigated factors. TND was the minimum distance from the base of the NAC to the nearest lesion margin. An increase in TND was associated with a decreased risk. Data showed that the mean TND was 2.0 cm for NAC-positive tumours and 4.7 cm for NAC-negative tumours.[13] Nevertheless, the best cut-off values of TND varied. Most authors suggested that the cut-off value should be set at ≥2 cm.[11,25,26] However, Sacchini *et al*. and D'Alonzo *et al*. supported a 1 cm cut-off value according to their reports.[16,27] There was no consensus on which imaging method was the best for TND evaluation. Billar *et al*. showed that mammography was the best imaging

Table 1: Incidence of NAC involvement in breast cancer in recent years (2008-2012)

Studies	*n*	NAC involvement (%)	Cases include		Section methods		
			Clinically involved nipples	LCIS	Distance from nipple base (mm)	Interval (mm)	Direction
Loewen *et al.*, 2008[14]	302	10.0	Yes	No	10-15	2-3	NR
Rusby *et al.*, 2008[15]	130	24.6	No	No	3	3	Coronal
Brachtel *et al.*, 2009[11]	232	21.0	No	Yes	3	NR	Coronal
Billar *et al.*, 2011[13]	392	16.0	Yes	Yes	NR	NR	NR
Weidong *et al.*, 2011[18]	2323	14.2	Yes	Yes	5	NR	Sagittal
D'Alonzo *et al.*, 2012[16]	100	14.0	No	Yes	4-5	1	Sagittal
Sakamoto *et al.* 2013[17]	81	21.0	Yes	Yes	NR	1-3	Sagittal/coronal
Wang *et al.*, 2012[12]	787	9.5	Yes	Yes	NR	2-3	Vertical

NAC: Nipple-areola complex; LCIS: Lobular carcinoma *in situ*; NR: Not reported.

option for identifying NAC involvement, followed by MRI and ultrasound imaging.[13] Friedman *et al*. reported that MRI of the breast could reveal nipple involvement even when it was clinically unsuspected.[28]

Tumour size

Tumour size was another main relevant factor in NAC involvement. An increase in the diameter of the primary tumour was associated with an increased risk for nipple involvement. In a previous study, NAC-positive tumours were larger, with a mean size of 3.3 cm versus 2.5 cm for NAC-negative tumours.[13] A more recent study showed that only a tumour size >2 cm and a distance from the tumour edge to the NAC <2 cm on MRI maintained significance in the prediction of NAC involvement.[24] However, the eligibility for NSM has expanded over time to include more patients. Some authors believed that NSM could be performed safely for any tumour size as long as there was no clinical or imaging evidence of NAC or skin involvement.[29]

Lymph node status

In the view of anatomy, nipple areola region is considered to be a lymphatic basin. Lymph node status reflects tumour burden and is therefore associated with a higher incidence of NAC malignancy. Some studies have confirmed this hypothesis. Patients with NAC involvement were more likely to have positive lymph nodes on final pathology, a finding noted in 52% of the NAC-positive group but only 34% of the NAC-negative group.[13] In a review of nipple involvement, 24.4% of the cases in the lymph node-positive group had nipple involvement, whereas nipple involvement was present in only 10% of the cases in the lymph node-negative group ($P < 0.05$).[19]

Histological characteristics

Histological type and tumour grade were noted to affect NAC involvement in only a few studies. One article identified a 26% incidence of NAC involvement in invasive micropapillary tumours, which was significantly higher than the incidences reported for other tumour types.[18] Another study revealed a significantly higher incidence of nipple involvement in IDC with an extensive intraductal component (EIC) compared with IDC without EIC.[11] Grade III tumour was also found to be related to a higher NAC positive rate compared with lower-grade tumour.[11,12,26]

Estrogen receptor, progesterone receptor and human epidermal growth factor receptor status

Weidong *et al*. reported that there was a significantly higher nipple involvement rate in the estrogen receptor (ER)-negative group (15% vs. 10% in the ER-positive group) and progesterone receptor (PR)-negative group (14% vs. 10% in the PR-positive group).[18] Despite the large sample size, this remains the only study showing statistical significance regarding ER and PR status. Negative studies may have resulted from the relatively small sample sizes.

Human epidermal growth factor receptor overexpression was found to be associated with NAC involvement by Brachtel *et al*.[11] Another study generated a predictive table based on a mathematical model to predict the probability of tumour involvement of the NAC by using tumour location, tumour Her-2 status and nuclear grade. These factors are usually clear preoperatively with reasonable accuracy.[12]

Breast biopsy

Govindarajulu *et al*. used Mammotome biopsies of the ducts beneath the NAC to detect occult NAC involvement in breast cancer patients before surgery.[30] In that study, 7 of 36 breasts had a positive Mammotome biopsy, which was 100% correlated with histopathology of the mastectomy specimen. They suggested that Mammotome biopsy could replace traditional frozen sectioning and to be used as an alternative for NAC evaluation. In another study, the authors suggested that the use of clinical criteria alone (tumour size and TND) had a false-negative rate of 53.8% in predicting NAC involvement. When adding both subareola and nipple core biopsies to the clinical evaluation criteria, the false-negative rate decreased to 7.7%.[31]

Risk factors for nipple-areola complex involvement

According to the present studies, we categorised the risk factors for NAC involvement into three groups by evidence level [Table 2]. Risk factors with strong evidence which were supported by nearly all studies to increase the risk of NAC involvement, including: Clinical involvement of NAC (history or physical examination of nipple discharge, nipple retraction, palpable mass in nipple and nipple bleeding), TND ≤ 2.0 cm and a positive NAC biopsy. Risk factors with intermediate evidence: Tumour size ≥2.0 cm, pathological grade >2, positive lymph node and Her-2 (+). Risk factors with low evidence were indicated by individual studies and therefore needed more evidence. This group included negative ER and PR status, possibly, certain histological types (invasive cancer with EIC).

Although all of the pathology information could be obtained preoperatively by core needle biopsy or open biopsy before the final surgery, there was no data regarding the relationship between breast biopsy pathology results and nipple involvement in breast cancer. Further studies needed to be done on this topic to support this idea. Some authors also computed a NAC Involvement Score based on mammographic TND, pathological stage, and tumour size to distinguish between the presence and absence of

Table 2: Risk factors for NAC involvement categorized by evidence level

Strong	Intermediate	Low
Clinical evaluation of NAC involvement[13,24]	Tumour size ≥2.0 cm[13,24,29]	ER(−) PR(−)[18]
TND ≤2.0 cm[11,13,25,26,28]	Pathological grade >2[11,12,26]	Invasive cancer[18]
NAC biopsy (+)[30,31]	LN (+)[13,19]	EIC (+)[11]
	Her-2 (+)[11,12]	

NAC: Nipple-areola complex; TND: Tumour-nipple distance; LN: Lymph node; EIC: Extensive intraductal component; PR: Progesterone receptor; ER: Estrogen receptors; Her-2: Human epidermal growth factor receptor 2.

NAC involvement. However, the study was based on only 31 patients.[23]

Surgical approaches and pathological examination

After careful preoperative evaluations, selected patients undergo NSM. Various surgical incisions and reconstruction strategies have been described. Frozen section pathology during surgery can determine the surgical margins, while final pathology provides definite NAC status. However, there are no available standard protocols for surgical approaches or pathological examination.

Surgical techniques

Surgical NSM techniques could affect both the oncological safety and aesthetic outcome of patients. Although the lack of available published data precluded the recommendation of any specific surgical approach, a lateral, radial, lateral mammary fold, or inframammary fold incision appears to provide excellent access to the glandular breast tissue in all four quadrants, permits axillary exploration (and removal of axillary breast tissue), and preserves skin flap sensation.[32,33] With flap elevation, the entire breast tissue is excised, leaving 4–5 mm thickness of skin flap. Some support removing all ductal tissue of the nipple core, while some believe leaving 5 mm of glandular tissue behind NAC. Breast reconstruction is performed immediately following NSM and ranges from implants to autologous flaps. The employed reconstruction strategy depends on a general assessment of patient preference, as well as of the risks and benefits. However, the authors were not yet ready to offer NSM with immediate autologous breast reconstruction as their standard of care.

Frozen section analysis

Frozen section analysis serves as the standard to rule out NAC involvement. If frozen section analysis is positive, traditional mastectomy or skin sparing mastectomy (SSM) is recommended. Otherwise, the surgeon proceeds with NSM. Other patients will undergo permanent section evaluation and NAC will be ultimately removed only if the final pathology is positive due to potential false-negative results from frozen section analysis.[34]

The section protocols that were used intraoperatively varied. Wagner *et al*. used surgical clips or sutures placed on the circumference of the areolar margin at the 3, 6, 9, and 12 o'clock positions and a fifth marking clip or suture immediately underneath the nipple to evaluate perioperative pathology.[10] Vlajcic *et al*. noted a 4.63% false-negative rate of frozen section histology of the NAC base compared with definitive histology.[26] Another study showed that 11 of 157 (7%) cases exhibited NAC involvement, all of which were identified with intraoperative frozen section analysis with subsequent removal of the NAC.[35] Moreover, nipple core needle biopsies had also been performed to evaluate possible occult NAC involvement intraoperatively.[36]

Final pathological evaluation

Final evaluation protocols of paraffin-embedded tissue also varied among studies. The main concern was the definition of NAC involvement, that is, the amount of tissue associated with the NAC was different. As mentioned before, some studies emphasized the importance of removing all ductal tissue of the nipple core to ensure oncologic completeness[37] by sharp dissection or point diathermy.[38] Other studies suggested that leaving 5 mm of glandular tissue behind NAC was necessary to preserve its blood supply and decrease the NAC necrosis rate, and accepted that leaving breast tissue might result in a higher risk of LR or development of new disease.[39,40] However, the mean thickness of the skin flaps in mastectomy was 4–5 mm, which was at the level of the superficial fascia dividing the subcutaneous fat from the breast glandular tissue.[41] Recent data suggested that when performing a NSM, the dissection plane could be even closer to the base of the nipple, including the entire duct bundle, with a reasonably low risk of necrosis.[42]

Oncological outcome of nipple-sparing mastectomy patients

Multiple prospective and retrospective studies investigating LR in NSM have been conducted to address oncologic safety, which are summarized in Table 3. The LR for NSM ranged from 0% to 24%. All studies excluded clinically involved NAC. NAC could only be preserved when no malignant cells were identified at pathology evaluation, otherwise NAC was re-excised. However, due to various patient selection standards, treatment protocols, and follow-up time, the oncological outcomes of NSM patients were difficult to compare among studies.

Local Recurrence in nipple-sparing mastectomy

Most studies have demonstrated that there was no significant difference in LR, distant metastasis (DM), and overall survival (OS) between traditional mastectomy and NSM to treat primary breast cancer. Sakurai *et al*. conducted a cohort study with a median follow-up time of 78 months.[48] The probability of LR was slightly higher in the NSM cohort than in the mastectomy cohort, but no significant difference was found (8.2% vs. 7.6%, $P = 0.81$). Gerber *et al*. did not observe any difference between the LR, DM, and breast cancer-specific death between modified mastectomy, SSM, and NSM after a mean follow-up of 101 months.[25] On the other hand, some researchers found a LR that was different between radical mastectomy and subcutaneous mastectomy (1.3% vs. 3.8% at 5 years).[35] However, they did not observe any difference in the survival.[36]

Local recurrence in the NSM cohort often involved the nipple and/or areola, skin flap, and local lymph nodes, with NAC recurrence rates between 0% and 3.7%. NAC recurrence cases could be treated with NAC removal and had good prognoses.[47] The disease-free survival after NAC removal in the NAC recurrence cases was 93% at the 5-year follow-up, demonstrating that NSM was indeed an oncologically sound treatment for breast cancer.[48] However, OS after primary surgery was significantly worse in patients who suffered an early LR (<3 years after primary surgery) than in those who suffered a late LR (68% and 86%, respectively, $P = 0.03$).[9]

Table 3: Oncological outcomes of NSM patients

Studies	Year	Median follow-up (months)	Number of patients	LR (%)	NAC recurrence (%)	Metastasis (*n*)	Radiotherapy	
							Percentage	Time
Sacchini *et al.*[27]	2006	24.6	68	2.9	0	1	0	NA
Voltura *et al.*[43]	2008	18	31	5.9	0	NR	32.3	Pre- or post-operative
Benediktsson and Perbeck[9]	2008	156	216	24.0	NR	44	21.8	Postoperative
Paepke *et al.*[44]	2009	34	96	2.0	0	2	1	Postoperative
Sakamoto *et al.*[45]	2009	52	87	0	0	9	27	Postoperative
Gerber *et al.*[25]	2009	101	60	11.7	1.7	14	28	Postoperative
de Alcantara Filho *et al.*[35]	2011	10.38	157	0	0	1	0	NA
Jensen *et al.*[46]	2011	60.2	99	3.0	0	1	16	Postoperative
Petit *et al.*[47]	2012	50	934	3.9	1.2	NR	94.9	ELIOT
Sakurai *et al.*[48]	2013	78	788	8.2	3.7	0	0	NA
Coopey *et al.*[29]	2013	22	315	2.6	0	0	7.4	Preoperative

NAC: Nipple-areola complex; NR: Not reported; NA: Not applicable; ELIOT: Intraoperative radiotherapy with electrons; NSM: Nipple-sparing mastectomy; LR: Local recurrence; NA: Not available.

Role of radiotherapy in nipple-sparing mastectomy

Some authors have proposed that additional radiotherapy should play the same role as in breast conservative treatment, that is, reducing the LR risk in the remaining breast tissue. Petit *et al*. suggested the use of an electron intraoperative radiotherapy treatment (ELIOT) when the NSM technique was employed.[49] In their study, a total dose of 16 Gy of ELIOT was delivered intraoperatively in the region of the NAC. Good local control of the disease and satisfactory cosmetic results were observed. They also reported that in another ELIOT series of 516 cases, final histology revealed foci of carcinoma in 63 cases. While 7 of these 63 cases underwent secondary NAC removal, 56 cases in which the areolas were preserved did not develop LR after 19 months of follow-up.[50] In addition, Benediktsson and Perbeck reported that radiotherapy effectively reduced LR, with a LR of 8.5% among patients who underwent radiation therapy versus 28.4% among patients who did not undergo radiation therapy over a median follow-up period of 156 months.[9] In another study, a comparison between 800 patients receiving ELIOT and 201 patients receiving delayed irradiation was conducted, and no difference in survival was detected between groups.[51] Some studies questioned the necessity of radiotherapy due to the lack of difference in LR between their studies (which employed neither intra-operative nor postoperative radiotherapy) and other published studies.[48]

Conclusions

Based on current studies, NSM appears to be oncologically safe after careful patient selection and assessment of margins. Although many studies presented in this review reported acceptable levels of LR, the lack of retrospective long-term studies makes NSM a controversial option for breast cancer treatment. Currently, many issues associated with NSM remain unresolved, including the lack of standardised patient selection criteria and consensus regarding the operative approach, pathology protocols, and the role of radiotherapy in NSM. Heterogeneity of the results between studies means that additional well-designed prospective cohort studies are essential to answer these questions.

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