



Recent trends in nipple sparing mastectomy—a narrative review

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Background and Objective: Nipple sparing mastectomy (NSM) has become increasingly popular in recent years, both as a treatment for selected cases of breast cancer and for BRCA carriers in prophylactic and therapeutic use.

Methods: PubMed, EMBASE, CINAHL and Cochrane were searched for studies on NSM up till June 2020.

Key Content and Findings: Different incisions are indicated in different situations and the ultimate decision should be reached after a multi-disciplinary discussion. A common complication of NSM is nipple areolar complex (NAC) necrosis. Therefore, it is imperative for its blood supply to be preserved as much as possible. A deeper understanding of the breast vasculature would also be useful in planning future surgical approach. While NSM offers a superb cosmetic outcome, oncological safety should never be compromised. Short term oncological safety for NSM is evident in recently conducted studies. Three major parameters were evaluated including overall survival, disease-free survival (DFS) and local recurrence rates. In general, NSM is associated with high DFS and low recurrence. As such, carefully selected breast cancer patients and high-risk BRCA patients would benefit from NSM despite occult NAC malignancy being a concern.

Conclusions: NSM offers a non-inferior outcome to the conventional mastectomy in selected cases. In the future, randomised controlled trials (RCTs) would be useful in demonstrating the long-term oncologic safety of NSM in breast cancer and BRCA-carrier patients.

Keywords: Nipple sparing mastectomy (NSM); breast cancer; BRCA

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Introduction

Great advances have been made in breast surgery over the past century. In 1882, Halsted performed the very first radical mastectomy with clearance of all breast tissue, the pectoralis major and associated lymphatic tissue (1). This was then modified by Patey in the 1940s to preserve the pectoral muscles. To date, the modified radical mastectomy (MSM) remains to be the conventional approach to breast removal in breast cancer patients with axillary nodal

metastasis (2).

However, in recent years less aggressive measures are adopted for treatment of breast cancer patients. In the 1980's, Fisher first introduced the concept of breast conservation therapy (BCT), which was followed by the development of skin-sparing and nipple sparing techniques in the late 1990's (3). Notably, Hartmann's paper published in 1999 demonstrated superiority of nipple sparing mastectomy (NSM) in high risk patients with a 90% reduction in breast cancer development (4). Since

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Table 1 Methods of literature review

Items	Specification
Date of search	15 th June 2020
Databases and other sources searched	PubMed, EMBASE, CINAHL, Cochrane
Search terms used	Nipple sparing mastectomy; nipple areolar complex sparing mastectomy
Timeframe	Up until June 2020
Inclusion criteria	English; any study type
Selection process	Literature review were conducted by both authors

then, NSM has been performed frequently worldwide. We present this article in accordance with the Narrative Review reporting checklist (available at <https://abs.amegroups.com/article/view/10.21037/abs-21-45/rc>).

Methods

PubMed, EMBASE, CINAHL and Cochrane were searched for studies on NSM up till June 2020 (*Table 1*).

Literature review

Practices around the world

With the popularization of NSM, there have been multiple nation-wide studies highlighting its surgical and oncological outcome. More than 60 NSM series have been published since 2000, with the majority being major single center studies indicating acceptable rates of recurrence after NSM. To date, one of the largest studies was performed on 2,440 breast cancer patients receiving NSM between 1998 and 2013. This study showed 5- and 10-year DFS at 96.9% and 94.9% respectively, comparable to standard mastectomy techniques (5). In 2015, a study conducted on Italian populations showed that oncological outcomes were satisfactory with low rates of loco-regional recurrence (2.9%), NAC recurrence (0.7%), systemic recurrence (1%) and major surgical complications (4.4%) including NAC necrosis rate (around 4%) (6). There are some publications which review the application of NSM in Asian populations. A review conducted in Singapore shows that NSM is associated with a 5-year DFS of 90%, local recurrence rate of 4% and is therefore an oncologically safe procedure in selected patients with a relatively low complication rate (7). Another similar retrospective study was conducted in Hong Kong, which reflected a low recurrence rate of 4.1%

and no delay of NAC excision from nipple necrosis (8). Overall, data published from specialised single centres show promising oncological outcome for NSM.

Indications for NSM

Although there is no definite consensus on which patients are selected for NSM, there are some guidelines in place for such candidates. The ultimate goal of NSM is to achieve negative resection margin (R_0) without compromising cosmetic outcome. As such, a small tumour size of less than 3 cm, tumour at least 2 cm away from the areola-papillary complex (APC) and peripheral tumour are some of the suggested parameters for NSM (9). In addition to tumour size and location, tumours should be of low grade and not have any lymphovascular invasion, cutaneous involvement, axillary node metastasis, or human epidermal growth factor receptor-2 (HER-2) positivity (10). Essentially, all patients who are eligible for skin sparing mastectomy (SSM) could now be offered the alternative of NSM given that they fulfil the above criteria. Currently, patients with more advanced disease, large tumours or nodal-positive disease and prior radiation therapy may also be considered candidates for NSM (11-13). However, treatment modality should be individualized and depends on surgeon expertise and patient factors. In terms of patient factors, poor outcomes are associated with advanced age (>45 years old), active smoking, diabetes mellitus, hypertension, high body mass index (>30 kg/m²), previous radiation, macromastia (C cup or larger) and women with ptotic breasts (grade 2 or 3) (14,15). With the development of skin reduction techniques (16), simultaneous mastopexy and implant reconstruction (17), together with new incision techniques including a Wise pattern and bi-pedicle dermal flap (18), even ptotic breasts could undergo NSM. Recent studies have also shown some evidence to suggest that BRCA-carriers would benefit from

prophylactic NSM (19).

Frontiers in NSM: staged breast reduction

Previously, macromastia and breast ptosis were contraindications for NSM due to the increased predilection for ischemic complications (20,21). The main purpose of staged breast reduction is to combat such complications. By reducing the skin envelope and repositioning the NAC, the rates of NAC and mastectomy flap necrosis are significantly reduced. In 2019, a matched cohort study was conducted between staged-breast reduction and non-staged techniques. This showed that in patients with a large breast size, staged breast reduction prior to NSM was associated with significantly lower rates of flap necrosis (22). A newly published retrospective study in 2020 performed bilateral reduction and mastopexy followed by NSM with immediate reconstruction using free abdominal flaps on breast cancer or high-risk BRCA patients. Those who have undergone such an algorithm had clear margins in all cases, with minimal complications including NAC necrosis (partial 8.2% *vs.* complete 6.6%) and no flap loss in any of the cases (23). As such, staged breast reduction as a surgical technique is indicated in large and ptotic breasts (24). In addition, the timing of pre-mastectomy reduction is crucial. When performed in the same setting as a single-staged procedure, the vasculature to the skin would be disturbed, increasing rates of complications (25). Therefore, in general practice, NSM is generally planned for 3 months after reduction, with an average period of 5 months between stages. Some studies report a minimum of 4 weeks between stages, which give the additional benefit of having smaller, nodal-negative tumours or *in situ* carcinomas (26).

Techniques of NSM

Vasculature of the breast

The nipple areolar complex (NAC) is mainly supplied by vasculature stemming from the subclavian artery. Specifically, the main arterial supply to the medial aspect of the breast is via the perforating branches of the internal thoracic artery. Branches from the lateral thoracic and posterior intercostal arteries also provide blood supply to the breast (27). Instead of following the ductal system, these vessels follow a path between the skin and the breast parenchyma. In NSM, blood supply preservation is of a high priority as nipple necrosis is a well-documented

complication (28). Anatomical variation of vascular supply is frequently documented. Although most cases of NAC receive principal supply from the second intercostal perforator originating from the internal mammary artery, dual supply is also evident in some cases. A study conducted by Bahl reported considerably lower necrosis rates in dual-supply breasts, hence a lesser need for debridement. In the future, pre-operative MRI could be useful in the delineation of breast vascularity, and in the subsequent surgical planning of NSM (28,29).



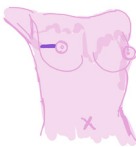

Different incisions for the NSM

There are numerous variations for incisions in NSM. Amongst these incisions, the four common ones are the peri-areolar, lateral, inframammary and vertical incisions (15). The characteristics of the different incisions are summarized in the *Table 2*.

Of note, the transareolar incision, which involves an incision bivalving the nipple from the medial and lateral sides, has yielded an exceptionally high NAC necrosis rate exceeding 80% (23). It has therefore become obsolete in recent times. According to a meta-analysis performed in 2019 (n=9,975), the inframammary approach has become the most popular incision, largely due to its acceptable cosmesis, suitability for single-stage reconstruction and low rate of NAC necrosis. In a recently conducted study, the inframammary fold NSM (IMF NSM) was shown to accommodate larger implants in relation to weight of the breast when compared to nipple sacrificing mastectomy in implant reconstruction with biological mesh. In comparison to the nipple sacrificing mastectomy group, the IMF NSM patients had no incidence of wound necrosis or threatened wound (30). However, not all cases are suitable for inframammary incisions, and the decision on the type of incision is still a multi-disciplinary opinion.

Novel approaches of the NSM include the robotic technique, which has limited data reflecting long-term outcome and remains to be in the assessment phase (31). Careful attention must be paid when selecting the method of incision as it also impacts on clinical outcomes, medical cost and aesthetic result. In a recently performed case-control study in 2020, the surgical margin involvement rate in both robotic-NSM (2.5%) and endoscopic-NSM (4.44%) were relatively low (P=0.52). The robotic-NSM showed superiority in satisfaction rate, cosmetic outcome, blood loss and surgical wound position in comparison to the endoscopic-NSM group (32). However, robotic-NSM

Table 2 Summary of common incisions for nipple sparing mastectomy

Incisions	Description	Advantage	Disadvantage	Risks of NAC necrosis	Target patient group
	Curvilinear incision along areola	(I) Well concealed scar; (II) adequate access to all breast quadrants; (III) good access for sentinel lymph node and axillary dissections	(I) Technical difficulty in performing; (II) low nipple areola complex sensitivity after surgery	Highest (18.1%) (disruption to the dermal vascular plexus)	Larger breasts or higher grade ptosis
	Linear incision from NAC directed inferiorly	(I) Ease of dissection; (II) precise inset; (III) setup for revision	(I) Higher wound healing issues in comparison to a mid-breast incision; (II) incision at least 6 cm to accommodate flap inset	Medium (incision lies between and runs parallel to medial/lateral mammary arteries)	Non-ptotic breasts Small breasts
	Linear incision from the lateral border of breast toward NAC	(I) Easy access to all quadrants of breast tissue, sentinel lymph node biopsy and axillary tail; (II) autologous reconstruction	(I) Obvious scar; (II) contraction results in nipple malposition; (III) flattening of the breast, particular after large tissue removal	Relatively low (less disruption to the subdermal vascular supply)	–
	Incision along the inframammary fold	(I) Well concealed scar; (II) excellent visualization and palpation of the underlying breast gland	Difficulty in accessing breast tissue in upper quadrants	Lowest (6.82%) (spares internal thoracic artery supply, may disrupt the hypervascular zone ant to the inf border of the pectoralis major)	Small breasted women

NAC, nipple areolar complex.

was also associated with a longer operation duration and higher medical cost (10,587+554 *vs.* 6,855+936 US dollars). According to a meta-analysis performed in 2019, endoscopic incisions have the lowest rates of NAC necrosis at 4.9% (33).

Oncologic safety of NSM—therapeutic NSM

As of the time of this publication, there are no published randomised controlled trials (RCTs) of NSM, with limited long term follow up in clinical series. There have, however, been multiple systematic reviews and meta-analysis performed on the oncological safety of NSM. In 2018, a systematic review was conducted which showed no difference between NSM and SSM in 5-year disease-free survival (DFS) and mortality rates. Similarly, local recurrence rates were acceptably low at 3.9% and 3.3% respectively (24). A further meta-analysis performed in 2015 showed that local recurrence and survival rates in NSM were comparable to MRM and SSM (25). In a systematic

review published in 2019, BCT was shown to be a feasible alternative to mastectomy in BRCA carriers owing to the non-inferior survival outcomes despite increase in local recurrence rate (33). These results are promising and institutions are now expanding NSM to include more patient groups. The low levels of recurrence and high rates of DFS are also echoed in more recent studies, with *Table 3* summarizing the relevant data in NSM (13,33-37).

At first glance, the results seem promising with low local recurrence and high DFS. However, the study conducted by Lago in 2018 showed that local recurrence is significantly higher. This could be attributable to the significantly longer follow-up time, even with a small sample size of 69 patients. The argument against NSM is formed on the basis that there is occult malignancy with NAC involvement. In fact, previous studies have indicated that there is NAC involvement in up to 58% (32) of NSM patients, with the overall rate at 11.5% (6). This is attributable to ductal and lobular cancers with terminal

Table 3 Oncologic safety of NSM

Study	Study type (size)	Follow-up time (months)	Overall survival (%)	DFS	Local recurrence (%)
2020, Parvez (33)	Cohort (n=175)	24	98.3	88.6%	4.6
2019, Frey (34)	Retrospective (n=496)	48	N/A	N/A	1.6
2019, Balci (35)	Retrospective (n=214)	62	N/A	DFS: 93.2% (TND <2 cm), 96.3% (TND ≥2 cm) at 10 years	4.7
2018, Li (36)	Retrospective (n=118)	53	92.4	DFS 91.5% at 3 years	3.4
2018, Lago (37)	Retrospective (n=69)	143	98.5	88.4%	11.6
2017, Smith (13)	Cohort (n=2,182)	51	N/A	95.7% at 3 years and 92.3% at 5 years	3.7

NSM, nipple sparing mastectomy; DFS, disease-free survival; N/A, not available; TND, tumor to nipple distance.

ductal lobular units (TDLUs). Nonetheless, there is strong evidence to suggest that NSM is associated with a low recurrence rate in carefully selected cases of sporadic breast cancer (8).

Applications of NSM in BRCA mutation carriers—prophylactic NSM

Cosmetic outcome may be particularly of concern as women with BRCA mutations requiring mastectomy belong to a younger demographic. However, BRCA mutation carriers are also at a higher predisposition of developing more aggressive disease (8), and oncological outcome should not be sacrificed for cosmesis. There is a role for prophylactic NSM in BRCA mutation carriers, as NSM offers superior cosmetic outcome. Previously, this role was small as there were limited studies published and published data do not have large sample sizes. In recent years, there has been an increase in popularity for NSM in BRCA carrier patients, with an increase in the relevant data sets. Recent data all demonstrated that no ipsilateral breast cancers occurred after prophylactic NSM in BRCA carriers (9,38).

Counselling of the patient for NSM

NSM offers superior cosmetic outcome and enhanced post-mastectomy body image. This has a positive impact on psychosocial well-being and self-esteem. However, the patient should be properly counselled prior to NSM and warned of the possible complications which may arise. Rates of skin necrosis could be up to 8%, and skin desquamation is not uncommon accounting for around 40% of cases. There is also a possibility for re-operation to deal with post-operative complications (10%), including implant

removal (3.4%). There is also a 5% possibility that nipple excision may be required, in cases where cancer is found at the nipple margin. Other complications include hematoma (3%), seroma and infection (6%) (38,39). This percentage varies between studies and surgeon experience, so the local statistic should be used for counselling of the patient in NSM (40).

Conclusions

NSM offers better cosmetic outcomes and non-inferior survival outcomes, in carefully selected patient groups with sporadic breast cancer and in BRCA mutation carriers. Further studies would be useful in elucidating the long-term sequelae of NSM in both BRCA carriers and sporadic breast cancer patient groups.

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