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ORIGINAL ARTICLE

Surgical and oncological safety of nipple-sparing mastectomy in an Asian population

Yvonne Ying-Ru Ng[1] · Veronique Kiak-Mien Tan[2] · Wan Sze Pek[3] · Jasmine Hui-Er Chang[1] · Yirong Sim[2] · Kong Wee Ong[2] · Wei Sean Yong[2] · Preetha Madhukumar[2] · Chow Yin Wong[1] · Yee Siang Ong[3] · Bien Keem Tan[3] · Benita Kiat Tee Tan[1]

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Abstract

Background Nipple-sparing mastectomy (NSM) allows for excellent postmastectomy reconstruction aesthetics and is used for both therapeutic and risk-reducing purposes. Reservations regarding the potential for locoregional recurrence and concerns about nipple–areolar complex (NAC) necrosis remain amongst many surgeons. We review the surgical and oncological outcomes after NSM in our institution.

Methods All NSM cases at the National Cancer Centre Singapore and Singapore General Hospital between 2005 and 2015 were reviewed. Tumour characteristics, reconstruction methods, surgical and oncological outcomes are described.

Results A total of 139 NSMs were performed for 130 patients. The median age was 46 years (range 21–66). The use of NSM increased from 2% of all breast reconstructions in 2005 to 37% in 2015. The majority ($n=119$; 86%) were for cancer treatment and 20 (14%) for risk-reducing purposes. Among those performed for cancer, patients mainly had early stage breast cancer ($n=106$, 89%). Autologous reconstruction ($n=111$, 80%) was most common. Early complications requiring surgical intervention occurred in 24 (17%) NSMs, including 9 partial/complete flap loss and 2 complete NAC loss. Smoking, previous breast radiation and periareolar incision were all not associated with a higher re-intervention rate ($p=0.93$, 0.41 and 0.91, respectively). Median follow-up was 43 months (range 5–145). Five patients (4%) developed local recurrence, including 2 NAC recurrences. The 2- and 5-year overall survival rate is 97 and 90%, respectively.

Conclusion NSM is an oncologically safe procedure in selected patients with acceptable low complication rates.

Keywords Nipple-sparing mastectomy · Immediate breast reconstruction · Asian

Introduction

The growing emphasis on attaining excellent aesthetic results without oncological compromise in the surgical management of breast cancer has led to the increasing popularity of nipple-sparing mastectomy (NSM) with immediate breast reconstruction as an alternative to the modified radical mastectomy or even the skin-sparing mastectomy in recent years [1–3]. While breast-conserving surgery (BCS) has become the preferred option in Western countries, mastectomy still remains the most frequent surgical option for the management of breast cancer in our population whether to attain sufficient oncological clearance or as a risk reduction strategy [4–6]. Nipple-sparing mastectomy allows for superior aesthetic outcomes as the preservation of the native skin envelop and the nipple–areolar complex (NAC) results in a natural breast form. It also obviates the need for nipple reconstruction [7–9].

Early reservations regarding NSM were two-prong with regard to local tumour recurrence and nipple necrosis. The main concern regarding the preservation of the NAC is the possibility of remnant occult tumour or a concentration of breast tissue that is at risk of developing a subsequent cancer [10]. Furthermore, perfusion of the preserved NAC is dependent on dermal perforators following NSM and hence

✉ Veronique Kiak-Mien Tan
veronique.tan.k.m@singhealth.com.sg

[1] Department of General Surgery, Singapore General Hospital, Singapore, Singapore

[2] Division of Surgical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610, Singapore

[3] Department of Plastics, Reconstructive and Aesthetic Surgery, Singapore General Hospital, Singapore, Singapore

susceptible to ischemia [11]. Wound complications may prolong recovery and delay commencement of adjuvant therapy if required. However, there is now increasing evidence suggesting NSM to be surgically and oncologically safe [3, 12–14]. While established as a contemporary surgical alternative to mastectomy for carefully selected patients in Western countries, there is limited literature documenting NSM utility and outcomes in Asia. This study reports our experience with NSM and immediate reconstruction at an Asian tertiary center. Primary end points are surgical and oncological outcomes.

Patients and methods

All NSM cases performed at the National Cancer Centre Singapore and Singapore General Hospital between 2005 and 2015 were reviewed. The decision for an attempt at nipple preservation is made by the breast surgeon after determining the absence of nipple involvement on breast imaging. Where necessary, additional imaging in the form of magnification views for the retroareolar region to assess calcification, or breast MRI, would be asked for. Strict contraindications to NSM include cancer involving the NAC and inflammatory breast cancer. Intraoperative frozen section histological assessment of the nipple base would be performed for all cases, and the nipple is preserved only when there is no malignancy or atypical cells evident. NSM was performed via 5 main incisions (periareolar with or without extension, omega pattern, inframammary fold, lateral or via a previous incision) based on the location of the cancer, presence of surgical scars, breast shape/volume and type of reconstruction planned.

Clinicopathological characteristics, operative details, surgical and oncological outcomes are recorded in a prospectively maintained database. Early complications occur within 30 days of surgery and are considered as a major complication if readmission to hospital and/or a second operation was needed. Late complications occurred at least 30 days after breast reconstruction. Local recurrence includes ipsilateral breast tumour recurrence including NAC, skin flap or chest wall. Regional recurrence includes ipsilateral axillary, infra/supra-clavicular or internal mammary lymphadenopathy. Distal recurrence involves metastatic breast cancer that has spread to other parts of the body. Disease free survival (DFS) time was determined from the time of curative surgery to the time of detection of tumour recurrence either clinically or on imaging. Overall survival (OS) was determined from the time of curative surgery to the time of follow-up or death. All patients were followed up by both the breast and plastic surgeons in the postoperative period.

Data were analysed using SPSS Statistics version 23.0 (IBM, Armonk, New York, USA). Categorical variables were investigated using the χ^2 test. $P < 0.05$ was considered statistically significant. This study had Singapore Health Services Central Institutional Review Board approval and was performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

Results

Between January 2005 and December 2015, 703 skin-sparing mastectomies with immediate breast reconstruction were performed, of which 139 (20%) were NSMs in 130 patients. Unilateral NSMs were performed in 121 patients, while the remaining 9 had bilateral NSMs. The median age was 46 years old (range: 21–66). Majority of the patients were Chinese (86%). Relevant patient and tumour clinicopathological characteristics are listed in Table 1.

NSM for cancer treatment was performed in 119 (86%) breasts and for risk-reduction purposes in 20 (14%) breasts. Amongst the NSMs performed for cancer, the majority had early stage breast cancer ($n = 106/119$, 89%). The median tumour size was 20 mm (range: 1–80). Majority of the 119 NSMs performed were for invasive ductal/lobular carcinoma ($n = 82$, 69%), while 36 (30%) had carcinoma-in-situ (CIS), and 1 (1%) was for primary malignant melanoma of the breast. Four patients (3%) had previous ipsilateral breast radiotherapy following previous BCS for breast cancer. Six patients (5%) had neoadjuvant chemotherapy prior to the operation. 52 (44%) and 19 (16%) patients had adjuvant chemotherapy and radiotherapy, respectively. 72 (60%) patients had adjuvant hormonal therapy. Some patients had cancer staging investigations performed postmastectomy and 2 of such patients were found to have distal disease to the lung and bone, respectively. The surgical incisions used for NSM depended largely on the breast shape and volume, tumour location, whether there was previous surgery or breast irradiation, and the type of reconstruction. In general, the incision should be oncologically safe, maximize NAC viability, and allow access to recipient vessels in cases where microvascular anastomosis are performed. Table 2 summarises the incisions for NSM and the type of breast reconstruction performed in this cohort.

Surgical outcomes

The median length of hospital stay was 8 days (range: 2–90). The total early complication rate was 24% ($n = 34$), including 9 (6.5%) partial/complete skin flap loss, and 15 (11%) nipple necrosis (Table 3). Twenty-four NSMs (17%) required a second operation. There was 1 (1%) complete flap (free DIEP flap) loss secondary to vascular inadequacy, and 2 (1.4%) complete nipple necrosis necessitating removal of the NAC. There was no association between NAC/flap complications

Table 1 Patient and tumour clinicopathological characteristics of patients who underwent NSM between 2005 and 2015

Characteristics of patients who underwent nipple-sparing mastectomy (NSM) ($n=130$)		
Median age, years (range)	46 (21–66)	–
Ethnicity		
Chinese	112	86%
Malay	4	3%
Indian	3	2%
Others	11	9%
Smoker		
No	98	75%
Yes	6	5%
Unknown	26	20%
Mean BMI (kg/m^2)	23.5 (16–37)	–
Total number of NSMs with breast reconstruction (n = 139)		
Indication for mastectomy ($n=139$)		
Therapeutic	119	86%
Risk-reducing	20	14%
Total number of NSMs for therapeutic indication ($n=119$)		
Type of primary cancer		
Ductal/lobular carcinoma-in-situ	36	30%
Invasive ductal carcinoma	76	64%
Invasive lobular carcinoma	3	2.5%
IDC special type	3	2.5%
Melanoma	1	1%
Median tumour size (mm, range)	20 (1–80)	–
AJCC tumour stage (pathological)		
0	36	30%
1	31	26%
2	39	33%
3	10	8%
4	2	2%
Others (melanoma)	1	1%
Previous ipsilateral radiotherapy	4	3%
Neoadjuvant chemotherapy[a]	6	5%
Adjuvant chemotherapy	54	45%
Adjuvant radiotherapy	20	17%
Adjuvant hormonal therapy	72	60%

[a]Excludes 1 patient who underwent prophylactic NSM for the ipsilateral breast included in our study, but had contralateral LABC and underwent neoadjuvant chemotherapy and skin-sparing mastectomy for contralateral LABC

and smoking ($p=0.93$) or previous radiotherapy ($p=0.41$). Furthermore, the type of skin incision also did not affect the development of NAC necrosis ($p=0.91$). Similarly, there was no association between the operation year (2005–2009 versus 2010–2015) and the development of NAC necrosis ($p=0.16$). Other early major complications include evacuation of breast hematoma ($n=3$, 2%), blocked drains requiring a change in theatre on postoperative day 1 ($n=1$, 1%), and strangulated small bowel secondary to herniation from a repair defect at the left rectus sheath donor site hence necessitating a laparotomy ($n=1$, 1%). The most severe complication in our study was general anaesthesia-related in a patient who developed an acute myocardial infarction complicated by a cardiovascular collapse immediately after the operation. She underwent an emergency percutaneous coronary intervention with stenting, developed acute pulmonary edema and required extracorporeal membrane oxygen support.

Late complications requiring a second operation for management more than 30 days after the primary operation occurred in 7 patients (5%) including fat necrosis to exclude carcinoma ($n=3$, 2%), breast abscess requiring implant removal ($n=1$, 1%), donor site hernia ($n=2$, 1.5%) and partial nipple necrosis that had failed conservative management requiring debridement ($n=1$, 1%) (Table 3).

Table 2 Type of incisions and reconstruction methods ($n = 139$)

Type of operation		
Nipple-sparing mastectomy (NSM) only	9	7%
NSM and sentinel lymph node biopsy	103	74%
NSM and axillary clearance	27	19%
Mastectomy incision		
Periareolar	93	67%
Periareolar +/− extension	91	65%
Omega pattern	2	1%
Radial	30	22%
Inframammary fold (IMF)	1	1%
Lateral (without a periareolar component)	12	8%
Previous incision (without a periareolar component)	15	11%
Unknown	16	11%
Type of reconstruction		
Autologous	110	79%
TRAM/DIEP/SIEA flap	80	
LD flap +/− implant	26	
TUG/PAP flap	4	
Expander/prosthesis only	28	20%
Lipofilling only	1	1%

Oncological outcomes

The median follow-up was 43 months (range: 5–145). Twelve patients (10%) had disease recurrence (Table 4). Five patients (4%) had local recurrence, of which 2 were at the NAC. The first patient with NAC recurrence had high-grade DCIS that was 10 mm in extent. Retroareolar tissue was negative for malignancy but the primary tumour bordered this retroareolar NAC tissue excision defect in the final mastectomy specimen. She had a DFS of 19 months before presenting with bloody nipple discharge. Tumour histology of the excised NAC showed DCIS. Similarly, the second patient had high-grade DCIS that was 15 mm in extent. Retroareolar tissue was also negative for malignancy and the primary tumour was 2 cm from the NAC. Likewise, she presented with bloody nipple discharge following a DFS of 98 months and the excised NAC histology was DCIS.

Two patients (1.7%) developed regional recurrence. The first patient had stage 2 invasive ductal carcinoma (IDC) (T2N0M0) with a DFS of 32 months before developing recurrence in the axillary nodes. The second patient had stage 1 IDC (T1N0M0) with a DFS of 19 months before developing regional nodal recurrence. Both patients had completed adjuvant chemotherapy following surgery for the primary tumour.

Seven patients (6%) eventually developed distant disease. Five patients had early stage breast cancer, 1 patient had stage 3 breast cancer and the remaining patient had primary malignant melanoma of the breast. Five of these patients had completed adjuvant therapy following resection of the primary tumour. There was no association between tumour recurrence and disease stage (early/late) ($p = 0.90$). At the end of the study, 5 patients (4%) had breast cancer-related deaths. The 2-year and 5-year OS rate are 97 and 90%, respectively.

Table 3 Surgical outcomes of nipple-sparing mastectomies ($n = 139$)

Median length of stay (days, range)	8 (2–90)	
Early complications (within 30 days of surgery) ($n = 139$)	34 operations	24%
Anaesthesia-related complications	1	0.7%
Nipple–areolar complex (NAC) necrosis	15	11%
Partial	13	9%
Conservative management	3	
Surgical management	10	
Complete	2	1.4%
Skin-related	15	11%
Minor bruising/skin dehiscence (conservative management)	6	
Partial flap loss requiring debridement	8	
Complete flap loss	1	
Breast/donor site hematoma requiring evacuation	3	2%
Others (operation-related)	2	1.5%
Readmission within 30 days	9	6%
Late complications requiring an operation ($n = 139$)	7	16%
Fat necrosis mimicking carcinoma	3	2%
Breast abscess requiring implant removal	1	1%
Donor site hernia	2	1.5%
Nipple revision	1	1%

Table 4 Oncological outcomes of nipple-sparing mastectomies

Median follow-up period (months, range)	43 (5–145)	–
Local recurrence ($n=119$)	5	4%
Nipple–areolar complex (NAC) recurrence	2	
Non-NAC recurrence	3	
Regional recurrence ($n=119$)	2	1.7%
Distant metastasis ($n=119$)	7	5%
Death ($n=130$ patients)	7	5%
Breast cancer related	5	
Non breast cancer related	2	
2-Year survival ($n=130$) Not applicable/lost to follow-up = 16	111/114	97%
5-Year survival ($n=130$) Not applicable/lost to follow-up = 67	57/63	90%

Discussion

The surgical management of breast cancer has evolved since Halsted's radical mastectomy to less mutilating options including the modified radical mastectomy and skin-sparing mastectomy which allows for immediate reconstruction [2, 4]. Throughout this progression, the emphasis has been on providing safe oncological outcomes while minimizing mutilating surgery. Nipple-sparing mastectomy pushes the boundaries further by allowing for improved aesthetic outcomes of immediate post mastectomy reconstruction, and has increasingly utilized for selected women who undergo mastectomy for either therapeutic or risk-reducing intent [12–14]. By retaining the entire breast skin and NAC, NSM retains the complete natural envelope for reconstruction by preserving the inframammary fold and nipple, and obviates the need for a further nipple reconstruction [7–9]. Advances in genetic profiling and the upward trend of prophylactic mastectomy also make NSM the preferred approach when performing mastectomy for risk-reducing intent [15, 16]. In our study, 14% of the NSMs performed were for risk-reduction. While NSM has gradually been accepted as a viable option especially in Western countries in select patients with the literature available to support its oncological safety, reservations regarding the immediate postoperative viability of the NAC that might delay adjuvant therapy, and the higher potential for LRR, are the primary hurdles to complete acceptance of NSM in our local population [3, 5, 12–14].

Uptake of postmastectomy reconstruction has increased in recent years due to available surgical expertise, elevated importance on aesthetics and awareness of the procedure and its good oncological safety [5]. Of the immediate breast reconstructions performed, our study demonstrated an increasing trend in NSM with a rise from 2% of all reconstructions performed in 2005 to 37% in 2015 (Fig. 1). This is in part attributed to robust data on the oncological safety of NSM from several studies [3, 12–14]. Likewise, we have managed to demonstrate that the 4% local recurrence rate (5/119) amongst our therapeutic NSMs (2 of which recurred at the NAC) was similar to the 4% (22/498) recurrence found in skin-sparing mastectomies with reconstruction in a prior study in our institution [5]. These low rates may be attributed to careful patient selection, good surgical techniques and routine intraoperative frozen section analysis of retroareolar tissue. Our results are comparable to that of other studies as demonstrated by a large multicentre NSM review conducted by Orzalesi et al. that found a low LRR at 2.9% and NAC recurrence at 0.7% out of 1006 cases [3]. Likewise, Frey et al. studied 319 women with 555 NSMs performed over a 9-year period with an average follow-up of 31 months and found the LRR to be 0.8% with no NAC recurrence [12]. Furthermore, Gerber et al. compared local recurrence

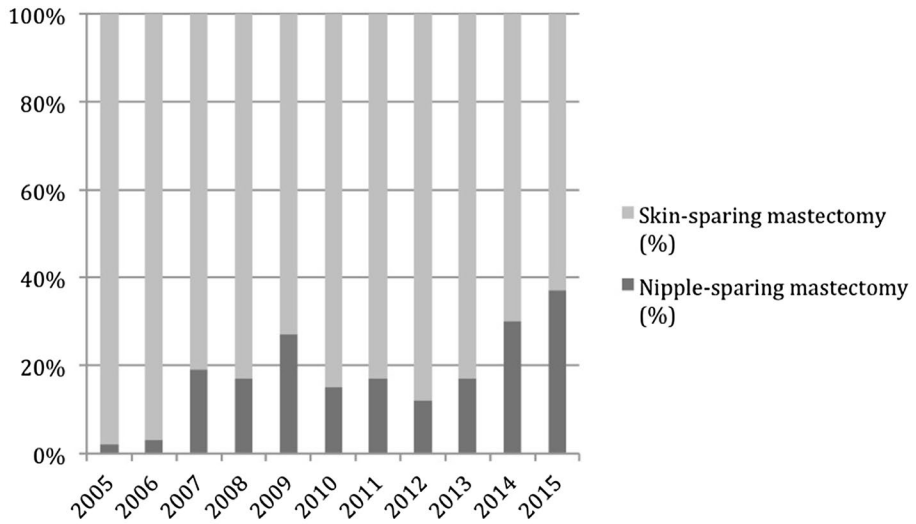

Fig. 1 Increasing trend of nipple-sparing mastectomy over the years

between modified radical mastectomy, skin-sparing mastectomy and NSM in 238 patients and found no significant difference in local recurrence between the 3 groups [18].

Several studies have attempted to identify clinicopathological characteristics associated with increased risk of NAC involvement and ensuing recurrence [3, 19–23]. Former relative contraindications such as tumour size, nodal status, and tumour to nipple distance < 2 cm appear not to diminish safety in NSM [19]. Orzalesi et al. found an association between tumours > 3 cm and that of tumour recurrence [3]. However, a propensity score-matched study by Agresti et al. shows that NSM may still be a valuable option for large breast cancer when a good response to primary chemotherapy has been achieved with no significant difference in 4 year local DFS in patients who underwent NSM versus conventional mastectomy [20]. Santoro et al. also demonstrated that neoadjuvant chemotherapy is not a contraindication for NSM [22]. In our study, 6 patients (5%) had preoperative chemotherapy for locally advanced breast cancer and we did not find any significant association between a late disease stage and tumour recurrence ($p = 0.90$). Recent studies have highlighted the role of MRI imaging in predicting occult NAC tumour involvement via studying breast duct anatomy and assessing the tumour to nipple distance [9, 21]. Ponzone et al. prospectively correlated MRI results with final pathological NAC assessment in 112 NSMs and found that a tumour to NAC distance ≥ 5 mm allowed for optimal discrimination between NAC positive and NAC negative cases [21].

The potential for threatened postoperative viability of the NAC as a result of thin skin envelopes and extensive undermining of the NAC to minimize nipple involvement or local recurrence is the second hurdle to acceptance of NSM [24, 25]. Asian women having relatively smaller breast envelopes after NSM than their Western counterparts that may predispose to skin envelope tension and hence skin and nipple necrosis compound this. Patient factors such as smoking due to direct skin vasoconstrictor effects of nicotine and medical comorbidities such as diabetes mellitus that predispose to poor wound healing have also been demonstrated to predispose to a higher complication rate [25]. Radiation before or after reconstruction has also been associated with increased complications as it decreases capillary density and dermal blood flow [26, 27]. In our study, none of the patients who were smokers or who had previous ipsilateral breast radiotherapy following BCS for breast cancer developed early complications requiring a re-intervention ($p = 0.93$ and 0.41, respectively). Apart from inferior cosmetic results and potential flap or implant loss, complications may also delay adjuvant chemotherapy or radiotherapy.

Despite these concerns, the reported rates of NAC necrosis are low between 2 and 20% and our study parallels this trend with a nipple necrosis rate of 11% with only 2 patients having complete NAC loss [3, 24, 26, 27]. Most of our NAC necrosis was partial, occurred within the first three postoperative weeks, and resolved with satisfactory cosmesis. NAC complications have also been associated with the type of skin incision [26, 28]. The lateral mammary skin crease incision is recommended as the incision of choice to minimize risk of NAC necrosis by some centres as it preserves the integrity of the blood supply while still allowing for complete breast removal with axillary clearance via a single incision. Regalo et al. demonstrated a 2.8% NAC necrosis rate via this incision [28]. In our institution, however, the periareolar incision with or without extension is most commonly utilized. This incision allows good surgical exposure during tissue dissection, removal of the subareolar tissue, and open access to the lateral margin of the pectoral major muscle for implant pocket dissection. Additionally, it was not significantly associated with NAC necrosis ($p = 0.91$). Preliminary studies with indocyanine green-based fluorescent angiography to aid intraoperative assessment of the mastectomy skin flap to guide excision of hypoperfused areas have shown promising results in decreasing the rate of flap necrosis and further studies should be performed to validate this [29, 30].

NSM was not frequently utilized in Asia until recently; hence data published by Asian centres are scarce. This study was designed to explore the surgical and oncological outcomes of NSM with breast reconstruction and with long-term follow-up data; our results are comparable to that of Western institutions. Future studies to assess the long-term aesthetics and patient satisfaction outcomes can be performed.

Conclusion

NSM has become a contemporary surgical treatment with increasing numbers being performed in our population over the past decade. It is an oncologically safe operation and is a suitable alternative to mastectomy for both therapeutic and risk-reducing intent.

Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to disclose.

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