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Risk Factors for Nipple-Areola Complex Involvement in Breast Cancer Patients: A Retrospective Study

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Abstract

Background: Nipple Sparing Mastectomy (NSM) has become a common procedure; but is not always suggested due to the theoretical risk of occult Nipple-Areola Complex (NAC) involvement. NAC involvement risk factors remain controversial. We aimed to confirm whether risk factors described in the literature should be considered as eligibility criteria for NSM.

Methods: This retrospective study analyses patients who underwent total mastectomy with immediate reconstruction for breast cancer at the Centre Antoine Lacassagne between January 2014 and December 2021. The primary endpoint was NAC involvement. The risk factors analyzed were extracted from the literature. The secondary outcome was the safety and feasibility of NSM compared to mastectomy without NAC preservation with immediate reconstruction.

Results: One hundred and fifty patients with NSM were compared to 100 patients without NAC preservation. We found a significantly higher rate of NAC involvement when the radiological Tumor-to-Nipple Distance (TND) was less than 2 cm (p=0.004). There was no significant difference concerning multifocality (p=0.53), tumor size (p=0.15), nipple discharge (p=1), clinical involvement (p=0.91), tumor localization (p=0.53), histological type (p=0.35), HER2/neu status (p=0.69), lymph node positivity (p=0.33) and lymphovascular emboli (p=0.74). We found no significant difference between the groups who underwent NSM and mastectomy without NAC preservation regarding the length of hospital stay (p=0.14), operating time (p=0.18) and postoperative complications (p=0.5).

Conclusion: NSM can safely be considered when radiological tumor-to-nipple distance is ≥ 2 cm if there is no pathological evidence of nipple-areola complex involvement. Further studies must be conducted to determine if a threshold of less than 2 cm can be considered.

Keywords: Nipple-sparing mastectomy; Nipple-areola complex involvement; Immediate reconstruction; Breast cancer

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Introduction

Over time, improvement in surgical techniques decreased the number of radical breast surgeries while maintaining similar if not better oncological outcomes [1,2]. Although conservative breast procedures remain the most performed surgery, some cases still require a total mastectomy. Nowadays, most women undergoing total mastectomy are eligible for immediate breast reconstruction. This allows for complete tumor removal while maintaining aesthetic outcomes.

Nipple Sparing Mastectomy (NSM) has a positive impact on quality of life with an impression of a less mutilating procedure [3]. Patients describe better psychological and sexual well-being with a quicker recovery [4]. Thanks to screening and improvement in imaging, breast cancer is associated with good long-term survival, making these aspects even more important.

The current issues remain the oncological safety and the complications of the NSM procedure. After more than 20 years of studies, NSM appears to be a safe oncological procedure for malignant disease in carefully selected patients [5-7]. Eligibility criteria are not well defined and the lack of standardized recommendations has a strong impact on surgical management.

According to the U.S National Comprehensive Cancer Network (NCCN) guidelines of 2022, NSM should be contraindicated in clinical or radiological Nipple-Areola Complex (NAC) involvement, Paget's disease, bloody nipple discharge associated with malignancy and inflammatory breast cancer [8]. Other criteria related to risk factors for complications such as active smoking,

obesity, prior wall irradiation, large and ptotic breasts are excluded in many centers [9,10]. It remains unclear whether previously described risk factors such as tumor localization and size, positive axillary lymph nodes, Human Epidermal Growth Factor Receptor 2 (HER2/neu) status, multicentric and focal tumor, Lymphovascular Invasion (LVI) and tumor-to-nipple distance are real risk factors for NAC involvement [11,12].

Based on the risk factors found in the literature, we assessed a cohort of patients who underwent a mastectomy followed by immediate reconstruction to identify risk factors for NAC involvement according to our experience. We also focused on complications between NSM and skin sparing mastectomy without NAC preservation followed by immediate reconstruction to ensure that NSM is a safe and feasible procedure.

Patients and Methods

Study population

The current study assessed all patients who underwent a total mastectomy with immediate reconstruction in the breast Surgery Department of the Centre Antoine Lacassagne, Nice, France from January 2014 to December 2021. From the CLINCOM database, using the code mastectomy and immediate reconstruction, we found 877 cases. Patients with synchronous distant metastasis, prophylactic mastectomy, neoadjuvant chemotherapy, clinical T4 disease and delayed reconstruction were excluded. After assessing the 283 patients' files meeting the inclusion criteria, 33 patients were excluded because of incomplete data. Finally, 250 patients were included in the study (Figure 1).

Data assessed

After the center's approval and the patients' consent, preoperative, intraoperative and postoperative data were recorded in the patients' medical files. The present study was written in accordance with the STROBE checklist [13].

The primary endpoint of interest was NAC involvement. In group A, we considered patients with pathological tumor-free NAC, while in group B, patients with NAC involvement were considered. The list of risk factors for NAC involvement was established based on the literature and international guidelines [8,11,12].

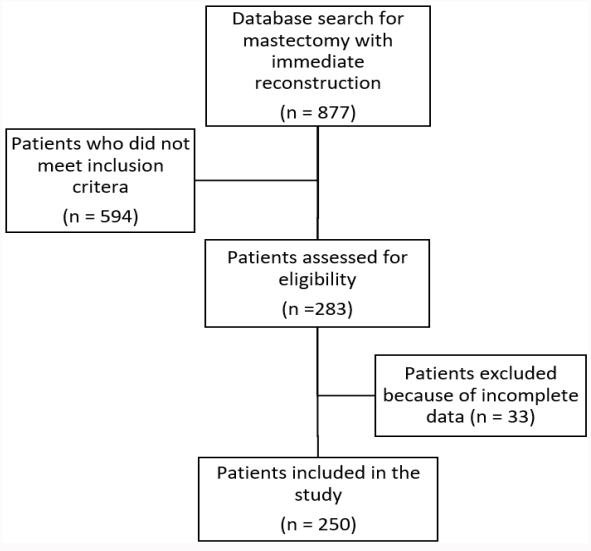

Figure 1: Study inclusion.

The secondary outcomes were the safety and feasibility of NSM compared to skin sparing mastectomy without NAC preservation with immediate reconstruction. Complications in both groups were taken one by one and crossed with general risk factors for surgical procedures and postoperative complications to decrease study bias.

Preoperative assessments were tumor size and localization, multifocality/centricity, clinical and radiological invasion of NAC, nipple discharge and radiological NAC-to-tumor distance evaluated by MRI and/or mammography and/or echography. In cases of multicentric or multifocal cancer, the lesion nearest to the nipple was used to assess radiological distance.

The intraoperative data collected were operating time and complications during the intervention. For bilateral cases, operating time was not included in the study.

Postoperative assessments were pathological tumor size, histological subtype, HER2 status, lymph node invasion, LVI, length of hospital stay and postoperative complications up to 3 months after the surgery.

In case of NSM, retroareolar section biopsy or marked retroareolar margin were used to determine NAC involvement. If the margin or the NAC biopsy were positive for carcinoma, the NAC was removed to confirm tumor invasion. In case of skin sparing mastectomy, we consider NAC involvement if the nipple or the skin was positive for carcinoma.

Patients underwent immediate breast reconstruction by prosthetic method or autologous latissimus dorsi flap.

Statistical methods

Patients' characteristics were assessed by the median in absolute and relative frequencies. Categorical variables were assessed using Pearson Chi square and Fischer exact test. Continuous data were compared using the unpaired t-test. A p-value lower than 0.05 was considered statistically significant.

Results

Patients' characteristics

Retrospectively, 250 patients who underwent a total mastectomy followed by immediate reconstruction were enrolled in the study. One hundred and fifty patients had pathological tumor-free NAC (group A), and 100 patients had NAC involvement (group B). The median age was 53 years (min 31 to max 81), the median Body Mass Index (BMI) was 22 kg/m^2 (min 17 to max 41.5) (Table 1). One-third of patients were smokers (n=68, 27.2%) and only 5 patients were diabetic (2%). One hundred and forty-six patients had a mastectomy without NAC preservation (58.4%) while 104 patients had NAC preservation (41.6%). Pathological TNM classification showed that three-quarters of the patients were T1c or more (74%). The axillary node status was mostly negative (64.4%). More than one-third of patients had a history of previous breast cancer (n=94, 37.6%) and almost all of them received prior homolateral breast irradiation (n=90, 36%). Postoperative median tumor size was 25 mm (range 1-150 mm). The histological subtype was Invasive Carcinoma of No Special Type (ICNST) in half of the cases (n=134, 53.6%), in situ carcinoma (n=79, 31.6%) and Invasive Lobular Carcinoma (ILC) (n=23, 9.2%). In 8 cases we found no residual lesion (3.2%) and other types cancer (phyllodes tumors and sarcoma) of cancer were detected in 6 cases (2.4%). There were no significant differences between

Table 1: Patients' characteristics (N=250).

Patients' characteristics	N=250
Age (years) *	53 (11.8)
BMI (kg/m^2) *	22 (6.4)
Tobacco use:	
non-smokers	140 (56%)
smokers	68 (27.2%)
former smokers	42 (16.8%)
Diabetes:	
Yes	5 (2%)
No	245 (98%)
Intervention:	
No NAC preservation	146 (58.4%)
NAC preservation	104 (41.6%)
Pathological TNM classification:	
T1a	13 (5.2%)
T1b	37 (14.8%)
T1c	54 (21.6%)
T2	76 (30.4%)
T3	55 (22%)
No residual tumor	15 (6%)
Negative axillary node	161 (64.4%)
Positive axillary node	40 (16%)
No axillary dissection	46 (18.4%)
Non-contributory examination	3 (1.2%)
Recurrence before mastectomy:	
Yes	94 (37.6%)
No	156 (62.4%)
Prior homolateral irradiation:	
Yes	90 (36%)
No	160 (64%)
Multicentricity/focality:	
Yes	146 (58.4%)
No	104 (41.6%)
Postoperative median tumor size (mm) *	25 (27.7)
Post-operative histological subtype:	134 (53.6%)
Invasive NST	23 (9.2%)
Invasive lobular	79 (31.6%)
In situ	8 (3.2%)
No residual lesion found	6 (2.4%)
Other type	
Hormonal receptor:	
Positive	138 (89%)
Negative	17 (11%)
HER2/neu status:	
Overexpressed	20 (13%)
Not overexpressed	134 (87%)

* Continuous data are presented as median (range); Non-Specific Type (NST)

group A and group B with respect to age, BMI, tobacco use, diabetes, prior recurrence before mastectomy, prior homolateral irradiation, palpable lump, postoperative histological subtype and postoperative median tumor size (Table 2).

Table 2: Comparison of patient's characteristics between patients with pathological tumor-free NAC (group A) and patients with NAC involvement (group B).

	Group A (n=150)	Group B (n=100)	p-value
Age (years) *	53 (11.8)	52.5 (11.7)	0.59
BMI (kg/m^2) *	22 (7.4)	22 (4.3)	0.15
Tobacco use:			
Non-smokers	92 (61.3%)	48 (48%)	0.08
Former smokers	24 (16%)	18 (18%)	
Smokers	34 (22.7)	34 (34%)	
Diabetes:			
Yes	4 (2.7%)	1 (1%)	0.65
No	146 (97.3%)	99 (99%)	
Recurrence before mastectomy:			
Yes	54 (36%)	40 (40%)	0.5
No	96 (64%)	60 (60%)	
Prior homolateral chest wall irradiation:			
Yes	53 (35.3%)	37 (37%)	0.8
No	97 (64.7)	63 (63%)	
Palpable lump:			
Yes	52 (36.2%)	32 (32%)	0.5
No	92 (63.8%)	68 (68%)	
NAC conservation:			
Yes	53 (35.3%)	7 (7%)	2.7
No	97 (64.7%)	93 (93%)	
Postoperative median tumor size (mm) *	30 (27.9)	22 (28)	0.8

* Continuous data are presented as median (range)

Risk factors for NAC involvement

More patients had a NAC involvement when the TND was <2 cm. The difference was significant with a p-value of 0.004. We found no statistical differences between group A and group B regarding tumor size, multicentricity/focality, clinical involvement, bloody nipple discharged, tumor localization, histological subtype, hormonal receptors and HER2/neu status, lymph nodes and lymphovascular invasion (Table 3).

Safety and feasibility of NSM

One hundred and forty-six patients underwent total mastectomy without NAC preservation followed by immediate reconstruction and 104 who underwent NSM. The characteristics of the two groups are described in Table 4. We found significant differences between the two groups regarding prior homolateral chest irradiation, the number of preoperative MRI performed and the axillary dissection.

The median operating time was 99 min in both groups. The length of hospital stay was 6 days after a total mastectomy without NAC preservation and 5 days after NSM (p=0.14). There were no intraoperative complications in either group. Regarding postoperative complications up to 3 months after the surgery, we found no significant difference between the two groups (p=0.5) (Table 5). The most common postoperative complication was NAC necrosis (n=12, 42.8%) in the NSM group and partial [14-16] or total

Table 3: Risk factors for NAC involvement compared between patients with pathological tumor-free NAC (group A) and patients with NAC involvement (group B).

	Group A (n=150)	Group B (n=100)	p-value
Post-operative tumor size:			
≤ 2 cm	56 (40,3%)	46 (48%)	0.15
2 cm -5 cm	53 (38.1%)	25 (26%)	
>5 cm	30 (21.6%)	25 (26%)	
Missing data	11	4	
Multicentricity/focality:			
Yes	90 (60%)	56 (56%)	0.53
No	60 (40%)	44 (44%)	
Clinical involvement:			
Yes	8 (5.4%)	5 (5%)	0.91
No	142 (94.6%)	95 (95%)	
Bloody nipple discharged:			
Yes	2 (2%)	1 (1%)	1
No		99 (99%)	
Tumor-to-Nipple radiological distance:			
≥ 2 cm	79 (52.7%)	33 (33%)	0.004
<2 cm	28 (18.6%)	30 (30%)	
Missing data	43 (28.7%)	37 (37%)	
Tumor localization:			
Central	16 (10.7%)	12 (12.1%)	0.7
Other	134 (89.3%)	87 (87.9%)	
Missing data	/	1	
Post-operative histological subtype:			
Invasive NST	82 (54.7%)	52 (52%)	0.35
Invasive lobular	10 (6.7%)	13 (13%)	
In situ	47 (31.3%)	32 (32%)	
No residual lesion found	6 (4%)	2 (2%)	
Other type	5 (3.3%)	1 (1%)	
HER2/neu status:			
Overexpressed	11 (12.1%)	9 (14.3%)	0.69
Not overexpressed	80 (87.9%)	54 (85.7%)	
Lymph node status:			
Positive	21 (17.7%)	19 (23.2%)	0.33
Negative	98 (82.3%)	63 (76.8%)	
Lympho-vascular invasion:			
Yes	16 (10.7%)	12 (12%)	0.74
No	134 (89.3%)	88 (88%)	
Hormonal receptors status:			
Positive	85 (92.4%)	53 (84.1%)	0.1
Negative	7 (7.6%)	10 (15.9%)	

NST: Non-Specific Type

skin flap necrosis (n=11, 32.4%) in the mastectomy without NAC preservation group. The other postoperative complications observed are described in Table 6.

Discussion

In the last 10 years, studies have proven that radiological Tumor-to-Nipple Distance (TND) is a key predictor of NAC involvement, showing an increased risk with decreasing TND [14-16]. However, using a TND threshold to consider a patient eligible for NSM remains controversial. A cut-off of >2 cm has often been used [3,17,18]. In our study, we proved that TND is a strong predictor for NAC involvement when TND is >2 cm. A safe TND threshold <2 cm could not be established because of the small number of patients having a TND of <2 cm (n=59). The following studies hypothesized that a TND of <2 cm should not be a contraindication for NSM. In a large series set in 2021, Wu et al. [19] found no significant difference in long-term oncological outcome between a preoperative TND ≤ 1 cm and >1 cm. Fregatti et al. [20] showed a significantly higher rate of excision margins when the TND was <2 cm but no significant difference in terms of loco-regional recurrence. To support this finding, Balci et al. [21] compared a group of patients with a TND <2 cm to one with a TND ≥ 2 cm. They demonstrated a NAC recurrence rate of only 1.69% when the TND was <2 cm and no significant difference between the 2 groups regarding locoregional recurrence and disease-free survival (10-years). These three studies specified that the NAC was removed in case of histopathology positive for carcinoma. That brings us back to the question of the prediction of the NAC involvement. MRI has shown a superiority to predict NAC involvement with a negative

Table 4: Comparison of patient's characteristics between patients who underwent skin sparing mastectomy without NAC preservation and NSM.

	Mastectomy without NAC preservation (n=146)	NSM (n=104)	p-value
BMI (kg/m^2) *	22 (4.8)	22.5 (8)	0.06
Tobacco use:			
Non-smokers	82 (56.3%)	57 (54.8%)	0.5
Former smokers	22 (15%)	21 (20.2%)	
Smokers	42 (28.7%)	26 (25%)	
Diabetes:			
Yes	2 (1.4%)	3 (2.9%)	0.6
No	144 (98.6%)	101 (97.1%)	
Recurrence before mastectomy:			
Yes	62 (42.5%)	32 (30.7%)	0.06
No	84 (57.5%)	72 (69.3%)	
Prior homolateral irradiation:			
Yes	60 (41.1%)	30 (28.8%)	0.04
No	86 (58.9%)	74 (71.2%)	
Preoperative MRI performed:			
Yes	82 (56.1%)	45 (43.3%)	0.04
No	64 (43.9%)	59 (56.7%)	
Type of reconstruction:			
Prosthesis (expander/direct implant)	121 (82,8%)	95 (91.3%)	0.05
Latissimus dorsi flap	25 (17,2%)	9 (8.7%)	
Axillary node dissection:			
Sentinel lymph node	96 (65.7%)	80 (77%)	0.04
Total dissection	19 (13%)	4 (3.8%)	
Previous node dissection	28 (19.2%)	15 (14.4%)	
No dissection necessary	2 (1.4%)	3 (2.9%)	
Node picking	1 (0.7%)	2 (1.9%)	

* Continuous data are presented as median (range)

Table 5: Comparison between mastectomy with and without NAC preservation.

	Mastectomy without NAC preservation (n=146)	NSM (n=104)	p-value
Post-operative complications:			
Yes	34 (23.3%)	28 (26.9%)	0.5
No	112 (76.7%)	76 (73.1%)	
Operating time (min) *	99 (57)	99 (44.3)	0.18
Length of hospital stay (days) *	6 (1.8)	5 (1.8)	0.14

* Continuous data are presented as median (range)

predictive value of 100% [15,22-24]. It is interesting to observe that in our center, the TND was missing data in 30% of the cases on the radiological report and that NSM was performed in less than half of the cases without MRI which these are crucial elements to guide our practice.

Our study showed no significant difference in NAC involvement with larger, multicentric/focal tumor, positive lymph node status and overexpression of HER2/neu. It remains unclear, in the literature, which recurrence risk factors can really be associated with NAC preservation. For example, tumor size, Ki-67 expression, LVI and positive lymph node status are risk factors for relapse that we can find in mastectomies with and without NAC preservation [12,25-27]. Patients with no clinical evidence of NAC involvement have an incidence of 11.5% of occult nipple malignancy [11]. Smith et al. showed a loco-regional recurrence rate of 3.7% but no recurrence involving the retained NAC among the 2,182 NSM performed [5]. Therefore, it is important to identify the NAC involvement risk factors to extend eligibility to NSM. NSM indication has recently have been extended to patients with more advanced diseases [9,28,29]. This is supported by our study which showed that one-third of the patients could have an NSM but did not. This is disregarding other risk factors of complication and the choice of the patient that could have guided our decision to a mastectomy without NAC preservation. On the other hand, we showed that 7% of the patients, who had an NSM, because we thought there was no NAC involvement, were finally invaded.

Bloody nipple discharge has been described in 2022 as a contraindication for NSM by the NCCN [8]. In our study, two out of three patients with bloody nipple discharge had no NAC involvement at the final pathological examination. The sample size in our study prohibits us from making a conclusion on this exclusion criterion. However, the absence of NAC involvement in this group raises the question of this contraindication and would require further study.

One of the most frequently reported complications of NSM is NAC necrosis. It is due to a lack of perfusion after removing the breast tissue [30-32]. Risk factors for postoperative complications include: diabetes, tobacco use, history of previous chest irradiation, elevated BMI, older age, and large and ptotic breasts which increase the risk of impaired skin flap and NAC perfusion [9,32-34]. We noticed a subtle trend of increased postoperative complications in the NSM group, compared to the mastectomy without NAC preservation group (26.9% *vs.* 23.3%), but it was not significant (p=0.5). We found a significant difference regarding the prior homolateral irradiation. In fact, fewer patients are offered NSM if they had a history of homolateral irradiation. Among the 28 patients who had a complication in the NSM group, 12 had NAC necrosis (11.5%), which was the most frequent NSM postoperative complication in our study. The median

Table 6: Postoperative complications observed after mastectomy with or without NAC preservation.

Postoperative complications	Mastectomy without NAC preservation (n=34, 23.2%)	NSM (n=28, 26.9%)
NAC necrosis	/	12 (42.8%)
Skin flap necrosis	11 (32.4%)	6 (21.4%)
Infection	9 (26.5%)	4 (14.3%)
Hematoma	7 (20.6%)	4 (14.3%)
Prosthesis exposure	6 (17.6%)	2 (7.2%)
Prosthesis malposition	1 (2.9%)	/
Removal of prosthesis needed	13 (38%)	6 (21%)

BMI of these 12 patients was 24.2 kg/m^2 (min 17.9 and max 30.4 kg/m^2), which was higher than that of the NSM group (22.5 kg/m^2). More than two-thirds of the patients who showed NAC necrosis were active smokers or former smokers and half of them had previous homolateral chest wall irradiation (n=6, 50%). The median age was 60 years, 9 years older than that of the NSM group. Treatment of NAC necrosis was local care for 3 patients, surgical NAC excision for 6 patients and prosthesis removal for 3 patients. Other complications observed were skin flap necrosis (n=6), infection (n=4), hematoma (n=4) and prosthesis exposure (n=2). Prosthesis removal was needed in 6 cases of complication after NSM (21.4%). In 4 cases the prosthesis was replaced by a breast expander and in two cases nothing could be done after the removal. In the skin sparing mastectomy without NAC preservation group, 13 prosthesis removals were needed after complications. In 7 cases, the prosthesis could be replaced by a breast expander, 1 case had a reconstruction by latissimus dorsi flap and in 5 cases the prosthesis could not be replaced.

Classifying postoperative complications in a reproducible way by treatment type according to the Clavien-Dindo classification, our study had 10 grade 1 complication (9.6%) and 18 grade IIIb complications (17.3%) [35]. Our complication rate could be explained by the inclusion of active smokers, elevated BMI, previous homolateral chest wall irradiation and older patients in our study. In the mastectomy without NAC preservation group, we observed 15 grade I complications (10.3%) and 19 grade IIIb (13%). It is interesting to note that, in both groups, we found higher rates of postoperative complications than the rate described by Clavien-Dindo (7.4% grade I and 4% grade IIIb) [35]. Our rate of postoperative complications after NSM is similar to the rates described in the literature [3,10,34].

We did not find a statistically significant difference regarding the length of hospital stay and the operating time between the two groups. NSM can be considered a safe and feasible surgical procedure.

The conclusions of this study should be interpreted with caution, for several reasons. Firstly, retrospective studies include biases of chart reviewing and have inherent limitations that are increased by the comparison of groups that are not made by propensity score matching. Secondly, a larger cohort of patients in the different categories could produce more accurate results. Thirdly, different radiologists were involved in the preoperative imaging and not all patients had a breast MRI, making it difficult to have an acute TND. A second lecture of the 30% of radiological missing data should be done in future investigations.

Conclusion

Our study confirms the hypothesis that radiological tumor-

to-nipple distance is a key risk factor for nipple-areola complex involvement. A threshold of ≥ 2 cm to safely offer a nipple sparing mastectomy has been determined in our study. However, a tumor-to-nipple distance of <2 cm should not be a contra-indication for performing a nipple sparing mastectomy. In that case, the patient should be informed of the risk of nipple-areola complex excision if positive retro-areolar margins are found in the definitive pathological examination. No differences were found between nipple sparing mastectomy and mastectomy without nipple-areola complex preservation regarding postoperative complications, operating time and length of hospital stay.

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