Nipple-sparing Mastectomy in Patients with Preoperative Diagnosis of Non-invasive Breast Carcinoma. A Single-center Experience

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Abstract. *Background: Nipple-sparing mastectomy (NSM) is a recognized treatment for selected patients with breast cancer (BC). Our study aimed to analyze 7 years' experience in NSM and breast reconstruction for patients with preoperative diagnosis of non-invasive BC. Patients and Methods: All NSMs with breast reconstruction, performed between January 2007 and December 2013 in patients with preoperative diagnosis of non-invasive BC, were considered. Results: Thirty-five NSMs were performed, 23 cases confirming the diagnosis of non-invasive BC, and in 12 patients it also resulted in findings of an invasive component. Patients were stratified into two groups: breast reconstruction was performed i) with silicone definitive implant, ii) with a temporary breast tissue expander. An invasive component at the postoperative histological examination was significantly associated with tissue expander reconstruction (p=0.03). Conclusion: In selected cases, NSM is a valid and safe procedure. Further critical evaluations are required for more evidence on this argument.*

The validity of a surgically-conservative therapy of breast cancer (BC) is internationally recognized (1-3). A patient's psychological distress after surgical treatment for BC has markedly decreased since the radical surgery shifted to breast conservation and immediate reconstruction (4). Skin-sparing mastectomy (SSM) with nipple-areola complex (NAC) excision and immediate breast reconstruction is a validated technique for the type of BC not allowing breast-conservative surgery, providing the best cosmetic result (5, 6). Success with SSM has paved the way for nipple-sparing mastectomy (NSM) as a valid alternative treatment to SSM and conventional mastectomy in selected patients (6-8).

NSM represents an ideal surgical treatment when it is applicable (7-9). Breast reconstruction after NSM is possible with satisfactory esthetic results, few complications and no decrease in the quality of life (10, 11). The entire breast skin envelope and the NAC remain preserved, allowing an immediate reconstruction and avoiding creation of a new NAC (8, 11, 12). In addition, patient psychological effects are improved (13).

Indications for NSM remain controversial (8,13), especially in those patients affected by non-invasive BC. This type of BC can be locally diffused, not well-evaluable at the preoperative assessment and the neoplastic tissue can be adjacent to the NAC, with a risk of recurrence (14).

Despite numerous studies on the validity of NSM procedures and immediate reconstruction (8, 15), the role of NSM in the treatment of non-invasive BC and the decision on the type of subsequent reconstruction are controversially discussed (16). Our retrospective study aimed to analyze around 7 years' experience in the treatment of patients with preoperative diagnosis of non-invasive BC who underwent NSM and subsequent immediate breast reconstruction with definitive breast implant or 2-step breast reconstruction, firstly with a saline-filled temporary expander and in a second step with breast definitive silicone implant. We evaluated our complications, outcomes and cancer recurrence rate to delineate internal guidelines.

Materials and Methods

Patients. A retrospective study was conducted considering patients with BC who underwent NSM in the period between January 2007 and December 2013 at the Department of Surgical Sciences, Sapienza University of Rome, Italy. According to the ethical standards of our Institution and of the Helsinki Declaration of 1975,

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Table I. *Patient characteristics and factors associated with breast reconstruction techniques after nipple-sparing mastectomy.*

	All patients	Reconstruction with definitive implant	Reconstruction with saline expander	*p*-Value
Number	34	16	19	
Age (years)‡	45.8±10.7	44.6±10.3	49.3±11.9	0.22
Breast ptosis (segment 3 >7 cm)	3	1	2	0.87
BMI (kg/m^2)‡	22.4±3.2	21.7±2.6	22.8±3.6	0.31
BMI ≥25 kg/m^2	5	3	2	0.84
BMI ≥30 kg/m^2	2	0	2	0.55
Menopause, n	12	4	8	0.48
Diabetes, n	1	0	1	0.93
Arterial hypertension, n	5	2	3	0.84
Smoker, n	4	3	1	0.47
Prior radiotherapy, n	3	0	3	0.29
Prior tumorectomy, n	6	2	4	0.82
Radial incision, n	29	13	16	0.83
Breast-fold incision, n	1	1	0	0.93
Vertical pattern, n	5	2	3	0.83
Carcinoma invasive component*, n	12	2	10	0.03
Implant infection, n	1	1	0	0.93

*At the definitive postoperative histological examination. BMI: Body mass index. ‡Mean±SD.

revised in 2000, patients with preoperative diagnosis of non-invasive BC and treated with NSM were considered. Patients with a breast-related cancer antigen (*BRCA*) gene mutation were also included. All patients were studied with radiological preoperative and clinical examinations. The preoperative diagnosis was obtained with percutaneous core-needle biopsy of the detected lesion. Patients were candidates for NSM if no infiltration of the NAC at imaging and no pathological nipple discharge were documented. All the patients were previously informed about the purpose and the possible complications and outcome of the nipple-sparing procedure, and their informed consent was obtained.

Surgical technical notes. The operations were performed using a radial incision (Figure 1), a breast-fold incision or a vertical pattern incision to allow skin-reducing procedure and correct breast ptosis. The NSM procedure was performed removing all visible breast tissue, as well as the glandular component located immediately behind the NAC. In all cases, an intraoperative histological exam with frozen sections of the areolar undersurface tissue was performed. Axillary lymph node staging was conducted with sentinel node biopsy procedure or radical axillary dissections depending on tumor size and definitive histological examination (17, 18).

The breast reconstruction was performed directly with breast silicone definitive implants or with breast tissue expanders, which required a second subsequent reconstructive step.

Assessment. We evaluated short-term postoperative complications assessment. In patients with a follow-up period longer than 5 years, it was possible to carry out a long-term evaluation including study recurrences and their management, and the patient's opinion of areolar sensitivity.

Statistical analysis. Patient characteristics were described using the mean±standard deviation for continuous normally distributed variables and percentage for dichotomous variables. Variables that were not normally distributed were described using the median with 25th and 75th percentile. Where applicable, Chi-square test and Student's *t*-test (two-sample) were used to calculate the *p*-values. A *p*-value lower than 0.05 was considered statistically significant.

Results

In the period between January 2007 and December 2013, 35 NSMs with breast reconstruction were performed in 34 patients with a preoperative diagnosis of non-invasive BC, obtained with percutaneous core-needle biopsy, at the Department of Surgical Sciences, Sapienza University of Rome, Italy. One patient presented a bilateral breast tumor hence she underwent bilateral NSM. Patient characteristics are reported in Table I.

Twenty-one tumors were located in the right breast, 14 tumors on the left side. At the postoperative histological examination, the definitive diagnosis of non-invasive BC was confirmed in 23 cases, and in 12 cases, an invasive component was also found. The mean size of the tumors was 15 mm (10-53 mm), including multifocal and multicentral type, and tumor recurrences.

Breast reconstructions were performed with saline-filled tissue expanders in 19 cases and with silicone definitive breast implant in 16 cases.

In all cases, an intraoperative histological examination with frozen sections of the under-areola tissue was performed. Only one of the NSMs was converted into SSM during the intraoperative time, based on the histological

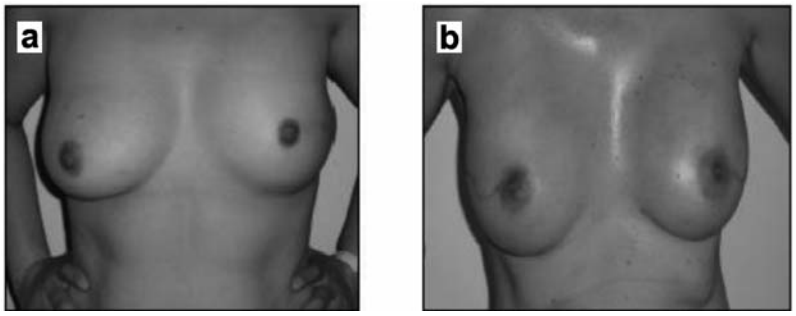

Figure 1. *a: Monolateral nipple-sparing mastectomy with radial incision. b: Bilateral nipple-sparing mastectomy. Both images were taken three months after surgery.*

analysis that was positive for the presence of tumor in the areolar flap's undersurface.

The sentinel node biopsy procedure was performed in the 12 patients with an invasive component, and in the cases of extended multifocal form of non invasive BC. In five patients, the sentinel lymph node was found to have a macro-metastasis and subsequently axillary dissection was performed, despite the preoperative imaging not revealing the suspicion of a lymph node lesion.

Only in one case the breast tissue expander was removed because of a peri-implant infection occurring in the postoperative period that caused necrosis and subsequent loss of the NAC. The patient was obese and a significant ptosis was detected in the preoperative assessment.

We stratified the patients into two groups, considering the breast reconstruction modality performed: one group in which the breast reconstruction was directly performed with silicone definitive implant, and a second group in which a breast tissue expander was initially positioned and the reconstruction was completed in a second step by replacement with a breast silicone implant to evaluate potential differences in complications, outcomes and cancer recurrence rate between the two groups

In univariate analysis, the two groups did not differ for any of the considered clinical parameters, except for the parameter "report of carcinoma invasive component at the postoperative histological examination", which was significantly associated with breast postoperative reconstruction using tissue expander (p=0.03) (Table I).

The mean follow-up postoperative period was 4.2 years (range=1-7 years). One patient with *BCRA* mutation experienced a pectoral skin metastasis 1 year after the NSM and subsequently, after 1 more year, a lung metastasis. One patient treated with NSM for a recurrence of breast tumor experienced a lung metastasis 2 years after the NSM. No recurrence at the NAC was documented. None of the patients self-reported as having sensitivity in the preserved NAC.

Discussion

The oncological validity of NSM is still controversial, mainly marked by the possibility of residual tumor cells in the NAC region and in the retro-areolar tissue after surgery (7, 11). However, there are studies that support the validity of conservative therapy and of NSM (1, 16). First of all, primary radical mastectomy does not improve survival rates (1). Randomized, prospective studies with extended follow-up periods documented no differences in overall survival in patients belonging to the mastectomy group whose NAC was removed compared to patients belonging to the tumorectomy group whose NAC was retained (14, 15).

In addition, studies with a small number of patients and a relatively short follow-up period found a low rate of recurrence within the NAC during 5 years of follow-up, suggesting that NSM is feasible in the setting of BC treatment, following precise indications, and helping to design further larger prospective studies to assess the oncological safety of NSM (19, 20).

There are several advantages of NSM. The psychological stress for the patient after breast amputation is markedly reduced. NSM allows breast prosthesis-based reconstruction in one single surgery, facilitating symmetry of the breasts. The breast skin envelope and the NAC are preserved, obtaining better cosmetic results than radical mastectomy, considering that the NAC is more difficult to reconstruct compared to the breast mound (11, 16).

For this reason, we retrospectively evaluated our experience in NSM and breast reconstruction modalities. We performed histological evaluation with frozen sections of the areolar undersurface tissue during each NSM procedure because it did not modify the surgical time. During the intraoperative time, waiting for the intraoperative histological result, we continued with the breast reconstruction. For our series of patients, one intraoperative resection of the NAC was performed because the frozen histological analysis was

positive for neoplastic cells in the undersurface of the areolar flap. In the other cases, the definitive histological examination confirmed the negative intraoperative evaluation and no secondary NAC resection for tumor was performed. As short-term complication, necrosis of the NAC due to peri-prosthetic infection occurred in one patient and consequently the NAC was secondarily excised. Regardless of the type of breast reconstruction pursued, no Mondor's disease was observed during the postoperative assessment, as described in other cases (21).

No recurrence of the tumor in the nipple area has been observed during the follow-up time in any patient of our cohort, although the mean follow-up period was 4.2 years, with a minimum of 1 year and maximum of around 7 years.

Periareolar incision has been described to be significantly associated with secondary necrosis of the NAC (11, 20, 22). In our series, no periareolar incisions were performed. Rarely did we choose a breast-fold incision, mainly performed during the first patients treated with NSM, because we saw that it could not ensure a complete glandular resection, especially at the level of the axillary extension. We preferred radial incision, which allows more wide control of the operative area and easy and rapid access to the axillary region when necessary.

At our clinical Unit, the indication for NSM follows several principles. The distance of the detected lesion from the NAC has to be 2 cm or more. An adequate preoperative evaluation is fundamental in order to investigate if hematic or abnormal nipple discharge and NAC or skin retraction are present, conditions that represent a contraindication for NSM (23). Moreover, we performed NSM according to tumor size in relation to the breast volume. In our series, the mean dimension of the tumor was 15 mm. Multifocal and multicentral tumor, and tumor recurrence after breast conservative surgery were considered. In small or small-to-medium breasts, the conservative excision of tumors of size around 2 cm can distort the original breast shape with unsatisfactory results from a cosmetic point of view. This suggested that in these cases it is worthwhile performing NSM and reconstruction in order to obtain better cosmetic results. This indication should not be considered for other types of BC such as sarcoma, although of the same size (24, 25).

We stratified the patients into two groups according to the breast reconstruction modality performed. We retrospectively analyzed the data discovering interestingly that breast reconstruction with tissue expander was significantly associated with the presence of an invasive carcinoma component at the postoperative histological examination. Evaluating the patients whose breasts were reconstructed with breast expander, the choice to perform the procedure in that way was driven by the suspicion at the preoperative imaging examinations of a possible invasive or microinvasive component of the BC.

In cases of non-invasive carcinoma, the location of the tumor can be more diffuse than the size obtained at the radiological examinations and more adjacent to the NAC, with a major risk of there being an invasive component of the tumor (2, 14), and with a long-term risk of local recurrence (11, 14).

Investigating our series of patients, we document that we strongly decided for breast reconstruction with tissue expander when the preoperative imaging showed lesions such as those suspicious for a possible invasive component of the tumor, confirming the data reviewed in other studies (16).

Conclusion

NSM is a valid alternative to SSM in selected cases and a procedure that allows better esthetic results compared to conventional mastectomy, without modifying the patient's overall survival.

Our retrospective study, although with the methodological limitations of a heterogeneous and limited series of patients with a mean follow-up period no longer than 4 years, documents that this proposed technique is valid and safe if performed selectively according to indications, but more observations are required for further critical evaluation.

Conflicts of Interest

No conflicts of interest to disclose.

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