



Surgical delay may extend the indications for nipple-sparing mastectomy: A multicentric study



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ABSTRACT

Introduction: Nipple-sparing mastectomy (NSM) is considered an oncologically sound procedure but necrosis of the nipple-areola complex (NAC) or skin flaps is a concern, particularly in the presence of risk factors. To increase the indications for NSM and decrease such complications, different procedures of “surgical delay” (SD) have been described.

Materials and methods: A retrospective analysis of patients who underwent SD for NSM at four Italian Breast Centers from 2014 to 2017 was performed. SD generally consisted of a periareolar or “hemi-batwing” incision, dissecting the skin and the NAC from the underlying breast tissue. NSM was scheduled after 2–3 weeks.

Results: Eighty-eight procedures were analyzed. Mild complications of SD were registered in 7.9% of cases. NSM was performed in 85 cases, whereas in three cases (3.4%) a “skin-sparing” mastectomy was necessary due to positivity of the retroareolar biopsy for cancer at SD.

A direct-to-implant (DTI) reconstruction was performed in 42 cases (49.4%), while in 43 (50.6%) a tissue-expander (TE) was inserted. After NSM, eight complications (9.4%) were recorded: one total necrosis (1.2%), one partial necrosis (1.2%) and four minimal ischemia (4.7%) of NAC, one skin flap necrosis (1.2%), one haematoma (1.2%). In only two cases (2.3%) prosthesis removal was needed. Aesthetic outcome was evaluated excellent or good in 92.9% of cases.

At a median follow-up of 24 months no local recurrences were seen.

Conclusion: This is the largest series of SD with NSM presented so far in the literature. In our experience, SD extends indications for NSM in high-risk women.

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Introduction

Nipple-sparing mastectomy (NSM) has been increasingly adopted in the past few years not only in the prophylactic setting but also in breast cancer surgery to improve cosmetic results and quality of life [1,2].

Early concerns about oncologic safety, especially regarding local recurrences in the nipple-areola complex (NAC), have not been confirmed by the vast majority of published experiences, even with long-term follow-up [3,4] and NAC recurrences have been registered in only 1.3% in a meta-analysis of 20 studies including 5594 patients. Similar rates of local recurrence, overall, and disease-free survival with NSM compared to other types of mastectomies have also been reported [5].

Oncologic safety of NSM has also been confirmed both in patients after neoadjuvant chemotherapy and in the prophylactic setting for BRCA-mutated patients [6–9].

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However, fear of NAC and skin flap necrosis has been a deterrent in high-risk patients, including those with large and/or ptotic breasts, previous surgery or radiation therapy, cigarette smoking or high BMI (Body Mass Index), because the risk of partial- or full-thickness necrosis in these settings varies from 7 to 17% [2,3,10–13].

Surgical delay (SD) techniques have been used for high-risk patients to improve the blood supply to the NAC through a compensatory mechanism, thus limiting complications and expanding indications for NSM [14–18].

A recent meta-analysis of five studies reported in the literature so far describes a total of 101 patients [12].

The purpose of this study is to report our multicentric experience with this approach.

Materials and methods

After IRB approval, all NSM performed in four Italian Breast Centers (Istituto Tumori in Milan, Asl Romagna Forlì, Asl Romagna Rimini, Azienda Ospedaliera San Giovanni-Addolorata in Rome) from October 2013 to October 2017 (in Milan from June 2016 to October 2017) were retrospectively reviewed. Patient data recorded were: age, smoking history and co-morbidities, previous breast surgery and/or irradiation history, breast volume and degree of ptosis according to Regnault classification [19]. Severe ptosis was defined as stage III of this classification.

A detailed informed consent was obtained in all cases and patient management was discussed both preoperatively and postoperatively in a multidisciplinary conference at each Institution.

SD was always carried out as an outpatient procedure under general anesthesia and usually performed through a “hemi-batwing” or a semicircular upper periareolar incision radially extended to external quadrants. All Centers initially employed the technique described by Jensen et al in 2012, dissecting the retroareolar and upper breast skin for 5 cm in all directions [15]. The incision was modified in some Centers as described in the results. In all cancer cases a retroareolar biopsy was obtained during SD and submitted for permanent pathology to analyze the eventual involvement of the retroareolar breast tissue by cancer prior to the scheduled mastectomy.

After a careful hemostasis, the skin was closed with an intradermal continuous absorbable suture and no drains were used.

In 24 (27.3%) cases a concomitant sentinel lymph node biopsy (SLNB) was obtained after Tc^{99m} lymphoscintigraphy or indocyanine green and submitted for permanent pathology.

Following SD an NSM was scheduled after 14–21 days. In the case of positivity of retroareolar biopsy, a skin-sparing mastectomy was proposed. In the case of positive SNLB, NSM was associated with axillary lymph node dissection.

In all DTI cases, a dual plain technique breast reconstruction was performed, covering only the upper pole of the implant with a pectoralis major and serratus anterior muscular flap.

Otherwise, in breast reconstruction with tissue-expander, the implant was placed in a total sub-muscular pocket.

Patient satisfaction was subjectively scored as excellent, good, sufficient and poor at six months.

Statistical analysis was performed using chi-square test. The level of significant was set at $p < 0.05$.

Results

From October 2013 to October 2017, 884 NSM were performed in four Italian Breast Centers. SD procedure preceded a scheduled NSM in 88 cases (9.9% of NSM) for 60 patients.

Median age of this group was 49 years (31–68).

Indications for NSM included breast cancer in 40 cases (45.4%)

Table 1
Tumor's characteristics.

Tumor features	Cases (%)
Histological type	
Ductal	37 (92.5)
Lobular	0
Other	3 (7.5)
T (at operation)	
T0	3 (7.5)
Tis	7 (17.5)
T1a	3 (7.5)
T1b	9 (22.5)
T1c	13 (32.5)
T2	5 (12.5)
Grading	
G1	4 (10)
G2	14 (35)
G3	22 (55)
Receptor status	
LLA	22 (55)
LLB	5 (12.5)
Neu+	5 (12.5)
Triple negative	3 (7.5)
Not evaluated	5 (12.5)

and prophylaxis for BRCA mutation in 48 cases (54.6%). Tumor features are reported in Table 1. SD was performed after neoadjuvant chemotherapy in 15 cases (17%).

Risk factors of the patients are summarized in Table 2.

A previous breast operation was registered in 28 cases (32%) and were seven lumpectomies, 15 quadrantectomies, three reduction mastoplasties and three additive mastoplasties. A previous periareolar incision (partial, total or enlarged) was present been performed in 18 of these 28 cases (64.3%).

More than one described risk factor was present in 20 cases (22.7%).

Main indications for SD were: severe breast ptosis in 54 cases (61.4%), previous surgery in 21 (23.9%), smoking habit six (6.8%), diabetes five (5.7%), and previous irradiation in two cases (2.2%).

Various approaches for SD were adopted by each group in this multicentric experience: an “hemi-batwing” incision and a semicircular upper periareolar incision extended to the external equatorial quadrants were performed in 40 (45.4%) and in 34 cases (38.6%), respectively. In 14 cases (16%) the incision was guided by a previous scar.

Median duration of SD was 58 min (± 20).

After SD no major complications were observed. We reported seven complications (7.9%); three (3.4%) minor epidermolysis of NAC, three (3.4%) hematomas not requiring surgical intervention and one (1.1%) minor ischemia of NAC that spontaneously recovered.

After SD, an NSM was performed in 85 cases (96.6%). In three out of 40 cases of cancers (7.5%), a retroareolar biopsy resulted positive for cancer and the procedure was converted to a skin-sparing mastectomy (SSM). In ten cases (11.8%) SLNB at SD was positive and NSM was directly scheduled with axillary node dissection.

Median operative time for NSM was 117.5 min (± 40).

Table 2
Risk factors of women submitted to surgical delayed.

Risk factors	N° of cases (%)
Breast ptosis	54 (61.3)
Smoking	13 (14.8)
Diabetes	4 (4.5)
Previous Surgery	28 (31.8)
Previous irradiation	12 (13.6)

Table 3
Complications of NSM after SD.

Complications	DTI (n = 42)	TE (n = 41)	Total NSM (n = 85)	P value
Epidermolysis	0	0	0	ns
Minor NAC ischemia (spontaneously recovered)	2 (4.8%)	2 (4.9%)	4 (4.7%)	ns
Partial NAC necrosis (surgical debridement)	1 (2.4%)	0	1 (1.2%)	ns
Total NAC necrosis	1 (2.4%)	0	1 (1.2%)	ns
Skin Flap necrosis	1 (2.4%)	0	1 (1.2%)	ns
Haematoma	0	1 (2.4%)	1 (1.2%)	ns
Total	5 (11.9%)	3 (7.3%)	8 (9.4%)	ns

DTI: Direct-to-Implant.

TE: Tissue expander.

Table 4
Complications of NSM of the entire series.

Complications	NSM Total (n = 884)	NSM without SD (n = 799)	NSM with SD (n = 85)	p value
Minor NAC ischemia (spontaneously recovered)	55 (6.2%)	51 (6.4%)	4 (4.7%)	ns
Partial NAC necrosis (surgical debridement)	25 (2.8%)	24 (3%)	1 (1.2%)	ns
Total NAC necrosis	19 (2.1%)	18 (2.2%)	1 (1.2%)	ns
Skin Flap necrosis	16 (1.8%)	15 (1.9%)	1 (1.2%)	ns
Haematoma	13 (1.5%)	12 (1.5%)	1 (1.2%)	ns
Infection	17 (1.9%)	17 (2.1%)	0	ns
Total	145 (16.4%)	137 (17.1%)	8 (9.4%)	ns



Fig. 1.



Fig. 2.

In 43 cases (50.6%) a two-stage reconstruction with a tissue expander was employed, whereas in 42 cases (49.4%) a DTI reconstruction was chosen.

Complications of NSM with SD described in Table 3. A comparison of complications observed in NSM performed by all four centers in the study period, with or without SD, is reported in Table 4. In only two cases with SD (2.3%), one total NAC necrosis and one skin flap necrosis, the implant was removed.

Women subjectively evaluated definitive aesthetic results as excellent, good and sufficient in 36 (42.3%), 43 (50.6%) and six cases (7.1%) respectively. None described aesthetic result as poor (Figs. 1–2).

Sensitivity of NAC was described as absent, partial or complete in 28 (33%), 45 (52.9%) and 12 cases (14.1%), respectively.

At a median follow-up of 24 months (± 16) no local recurrences were observed.

Discussion

We report the largest experience, to date, regarding SD aiming to extend the indications for NSM.

Our multicentric study confirms that SD is technically feasible

and major complications associated with these procedures (total NAC and/or skin flap necrosis) are infrequent (2.4%), even in a group of patients at higher risk.

In addition, SD allowed for an accurate preoperative assessment of the retroareolar margins in case of cancer or a definitive assessment of SLNB submitted for permanent pathology. In our experience this facilitated a better surgical planning, changing the indications from NSM to a skin-sparing mastectomy in 7.5% of cases or allowing a scheduled axillary node dissection at the time of NSM after a positive SLNB at SD (11.8% of cases).

A previous surgical incision was present in 28/88 cases (of which 64% were periareolar) and complication rate did not differ, suggesting that patients with previous breast surgery can be candidates for this approach.

The increasing appeal for NAC conservation during mastectomy due to an improved aesthetic outcome and a consistently low incidence of NAC recurrences evidenced in the literature have contributed to the widespread diffusion of NSM in recent years [1–3,10]. One meta-analysis showed that results after NSM do not significantly differ from other types of mastectomies (radical modified mastectomies and skin-sparing mastectomies) in terms of local recurrence, disease-free survival and overall survival,

although it has been reported that the findings from observational studies of low-quality evidence may be inconclusive due to high risk of selection bias [3,5].

Nevertheless, a recent report from European Institute of Oncology on 1989 consecutive patients with cancer treated in 2003–2011 with a median follow up of almost eight years has confirmed excellent oncologic results and that NAC recurrences are rare (1.8%) [20].

A major issue regarding NSM remains the potential for ischemic complications of the skin envelope of the breast and NAC which may potentially compromise aesthetic results, prolong recovery time and delay the appropriate timing for beginning of adjuvant therapies [13,21–23].

In a prospective study of 606 consecutive mastectomies, both NSM and specimen size were significant risk factors for skin flap necrosis on multivariate analysis. The authors concluded that complication rates after this procedure are likely higher than those reported in retrospective series and that patients with multiple risk factors should receive appropriate counseling if they are contemplating NSM [11].

However, there is evidence that such complications are decreasing with time as underlined in a systematic review of 12,358 cases most likely due to improved experience [4].

In addition, the type of surgical incision [24], the preservation of the perforating vessels of the internal mammary artery [25], the use of intraoperative evaluation of indocyanine green angiography [26] and the thickness of skin flaps have all been reported to play a major role in the prevention of ischemic complications [4].

While we believe that performing an accurate NAC dissection with uniform thin skin flaps allows for a complete and adequate resection of the breast gland and minimizes the chance of local recurrences, risk factors such as smoking, obesity, previous breast surgery and irradiation or large and ptotic breasts are shown to be associated with NAC or skin flaps necrosis in up to 17% of cases [13].

SD techniques have been proposed to improve blood flow to the NAC from the surrounding skin once it has been dissected from the breast gland. During the interval between SD and NSM (usually 2–3 weeks), vascular patterns of NAC and surrounding skin are deeply modified. A study with indocyanine green angiography has shown that vascularization of the NAC in severely ptotic breasts derives predominantly from the underlying gland; after surgery, this pattern changes, resulting in an inflow from the surrounding skin. This is probably due to the development of new microvessels as a result of the surgically-induced ischemia [17].

The physiological mechanism of this phenomenon, studied particularly in plastic surgery for many years, is not completely understood, but undoubtedly the stimulation created by the surgical wound and the vascular “shunt” lead to the release of growth factors, cytokines and other metabolites which stimulate angiogenesis and improve vascularization [12,15].

SD was first proposed in a short report in 2004 and since then different techniques have been described [14,15,17,18,21,27–29].

While we initially adopted the classic approach described by Jensen et al. using a “hemi-batwing” incision we progressively modified this technique with the use of a semicircular periareolar incision extended laterally to allow a more comfortable reconstruction by the plastic surgery team, thus enabling a more precise resection of the excess skin of the upper breast and a correct positioning of the NAC at the time of NSM.

Type of reconstruction may represent a further issue regarding complications after NSM and a recent meta-analysis of outcomes following DTI vs. two-stages reconstruction with a tissue expander in case of mastectomy showed an higher risk of complications with the former [30].

Lastly, a variety of other factors must be accounted for in the

planning of this procedure and surgeons have adopted different techniques to decrease tissue damage, such as the use of radio-frequency blades, or the pre-operative ICG study [17,28].

An alternative staged NSM technique following mastopexy or reduction for patients with ptotic breast was proposed by Spear et al., in 2012 [31] with a very variable time from first stage to NSM (one months to 10 years). Complications observed (skin flap necrosis rate of 17%, partial nipple-areola complex necrosis and 4% device explantation rate) were within the published range of immediate breast reconstruction assisted with acellular human dermis.

Our study has some limitations. First, it is a retrospective review, involving different centers with different indications, both for SD and NSM. Second, surgeons involved in our study used different techniques over time which were not standardized before the study.

However, this is a large, multicentric experience which may eventually better represent an average scenario in clinical practice and therefore our report may help clinicians in using this technique.

In conclusion, we believe that in women with known risk factors who must undergo a mastectomy, SD may enlarge indications for NSM and, although it implicates a two stages intervention with a subsequent potential delay in final timing of recovery, is a powerful tool to maintain low complications rates in a setting of patients as those included in our report.

Further studies are needed to confirm these results and to evaluate indications and techniques, and we are currently promoting a national registry to collect prospective data regarding the results obtained with this new technique.

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