Nipple-Sparing Mastectomy with Primary Implant Reconstruction: Surgical and Oncological Outcome of 435 Breast Cancer Patients

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Keywords

Breast cancer · Nipple-sparing mastectomy ·
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Summary

Background: This study aimed to examine the incidence of surgical complications associated with nipple-sparing mastectomy (NSM) with primary implant reconstruction, analyze risk factors for early and late surgical complications of NSM, and determine the incidence of local recurrences and the safety of sparing the nipple-areola complex (NAC). **Methods:** This retrospective cohort study included 435 patients with 441 NSM procedures over a period of 9 years (2004–2012). All surgical complications and the oncological outcome were recorded during follow-up. **Results:** The most common early surgical complication was skin flap ischemia/necrosis (26 patients, 5.9%). Prosthesis explantation due to complications was carried out in 11 (2.5%) cases. Neoadjuvant chemotherapy, implant size >500 ml, diabetes mellitus, body mass index > 25 kg/m², and incisions other than lateral were risk factors for early complications ($p < 0.001$). The NAC excision rate was 5.4% (24 cases) due to confirmed presence of cancer cells in the subareolar tissue. Capsular contracture as a late complication occurred in 33 (7.48%) cases. Local relapse occurred in 32 (7.3%) patients. Distant metastases were diagnosed in 68 (15.6%) patients, and 53 (12.2%) patients died during the follow-up period. **Conclusions:** NSM with immediate implant reconstruction has an acceptable morbidity rate

and is an oncologically and surgically appropriate treatment for most women requiring mastectomy.

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Introduction

Nipple-sparing mastectomy (NSM) has been proven to be an oncologically safe procedure in breast cancer surgery [1–4]. With primary implant reconstruction, NSM has become the best treatment option for women requiring mastectomy due to better cosmetic result, greater satisfaction, and better quality of life compared to modified radical mastectomy or skin-sparing mastectomy [5, 6]. Breast reconstructions are subject to possible early postoperative complications related to either wound healing or flap viability that can lead to prolonged convalescent periods, albeit without causing significant delays in adjuvant chemotherapy or radiotherapy [7–9]. Although rare, serious complications usually require another surgery and can lead to implant loss. The procedure appears to be oncologically safe for appropriately selected patients, but additional long-term follow-up is needed especially in patients with advanced stages of disease [10].

This study presents a single-institution experience in primary breast reconstruction with implants following NSM. Our aims were to examine the incidence of surgical complications of NSM with primary implant reconstruction, analyze risk factors for early and late surgical complications of NSM, and determine the incidence of local recurrences and the safety of sparing the nipple-areola complex (NAC).

Material and Methods

This retrospective cohort study was approved by the ethics committee of the Oncology Institute of Vojvodina and included 435 patients (6 with bilateral surgery) with 441 NSM procedures over a period of 9 years (2004–2012). The study included breast cancer patients with NSM and primary reconstruction performed as initial procedure or after previous breast-conserving surgery (BCS) or neoadjuvant chemotherapy.

Before surgery, patients were counselled about the procedure, oncological safety, risks of early and late complications, risk of NAC removal in the case of cancer cells being detected in the tissue beneath the nipple, and postoperative esthetic expectations. Routine preoperative diagnostics included clinical examination, ultrasonography, mammography (magnetic resonance mammography in some cases), and core biopsy.

Mastectomy was usually performed via lateral incision (358 cases, 81.2%) extended to the upper outer quadrant, thereby allowing axillary access for sentinel node (SN) biopsy or axillary clearance. Other types of incisions were used only in cases with previous excisional biopsy or BCS in an attempt to incorporate the previous incision into the NSM incision (83 cases, 18.8%).

The breast volume, consisting of the breast tissue and fat, was entirely removed, except for the part under the NAC. Subareolar tissue was excised and sent off for frozen section analysis. The NAC was preserved when no malignant cells were identified in the frozen sections.

Primary breast reconstruction was performed with contoured profile gel-filled prostheses (Mentor Contour Profile®, fixed-volume implants; Irvine, CA, USA) placed into the muscle pocket formed by the pectoralis major and the serratus anterior muscle. The goal was to maintain the natural breast contour, volume, and position.

For tumors smaller than 3 cm, and in some cases of high-grade ductal carcinoma in situ (DCIS), SN biopsy was performed as standard procedure with intraoperative frozen section analysis. Axillary clearance (levels I and II) was performed if SN biopsy revealed metastases and in all cases of invasive multicentric breast cancers, tumors over 3 cm, and local recurrences after BCS with previously performed SN biopsy. If NSM was performed due to local recurrence after previous BCS with axillary clearance, staging was assessed according to the histopathology of the first operation.

In the case of minor complications, patients were followed up every week after hospital discharge. Regular follow-ups by the surgeon and the medical oncologist were carried out every 3 months during the first year, and then every 6 months during the second and the third year. Thereafter, appointments for check-ups were made once a year.

All early and late surgical complications and the oncological outcome were recorded. Skin flap ischemia/necrosis <2 cm² was recorded as a minor event, while larger areas of ischemia/necrosis were regarded as a major complication. Infections treated with oral antibiotics were rated as minor, while those requiring parenteral administration of antibiotics were considered major infections.

Statistical analysis was performed with SPSS v.16 (IBM Corp., Armonk, NY, USA) using t-test for continuous variables, Kaplan-Meier for overall survival estimates, and Pearson's chi-squared and Fisher's exact test for categorical variables assuming that the results for the 2 breasts of the same woman are independent. The level of significance was set at 0.05.

Results

The mean patient age was 49 years (range 25–75 years, standard deviation (SD) 9.59); the mean follow-up period was 79 months (range 34–141 months, SD 27.7).

Surgery was the primary treatment for breast cancer in 252 (57.93%) patients. 117 (26.9%) patients were operated on after neoadjuvant chemotherapy, while 66 (15.17%) patients had previously received BCS followed by adjuvant treatment (radiotherapy with or

Table 1. Indications for nipple-sparing mastectomy (NSM)

Indication for NSM	n (%)
Size of invasive cancer (tumor/breast size ratio)	117 (26.5)
Multicentric cancer	194 (44)
Extensive ductal carcinoma in situ (DCIS)	23 (5.2)
Local recurrence after breast-conserving surgery	67 (15.2)
Invasive cancer + DCIS	40 (9.1)
Total	441 (100)

Table 2. Staging and treatment

Variable	n (%)
<i>Stage</i>	
0	22 (5.1)
I	95 (21.8)
IIA	102 (23.4)
IIB	95 (21.8)
IIIA	80 (18.4)
IIIB	18 (4.1)
IIIC	23 (5.3)
<i>Tumor histology</i>	
Ductal	309 (70.1)
Lobular	89 (20.2)
Other	43 (9.1)
<i>Axillary evaluation</i>	
Sentinel lymph node (SN) procedure	55 (12.5)
Axillary dissection	313 (71)
Axillary dissection after SN biopsy	21 (4.8)
Not assessed (some cases of ductal carcinoma in situ)	12 (2.7)
Previous axillary clearance during breast-conserving surgery	40 (9.1)
<i>Nipple-areola complex removal</i>	
Yes	24 (5.4)
No	417 (94.6)
<i>Neoadjuvant chemotherapy</i>	
Yes	117 (26.5)
No	324 (73.5)

without adjuvant chemotherapy) and were undergoing surgery due to local recurrence. Implant sizes were between 120 and 775 ml (mean 347 ml, median 345 ml, SD 144.9).

Indications for mastectomy are presented in table 1, and stage and treatment in table 2.

An SN procedure was carried out in 77 patients, with 56 SN-negative and 21 SN-positive patients requiring axillary clearance. Overall, axillary clearance was performed in 334 (75.7%) patients, and in 51 (11.56%) cases clearance had been performed during previous BCS.

Fig. 1. Kaplan-Meier curves showing the probability of overall survival for patients after nipple-sparing mastectomy (NSM).

Table 3. Early and late complications of nipple-sparing mastectomy

Complication	Procedures, n (%)
No complication	377 (85.4)
Epidermolysis	2 (0.5)
Nipple-areola complex necrosis	1 (0.2)
Minor infection	8 (1.8)
Major infection	7 (1.6)
Minor skin ischemia/necrosis	11 (2.5)
Major skin ischemia/necrosis	12 (2.7)
Prolonged seroma formation	13 (2.95)
Wound dehiscence	1 (0.2)
Hematoma	3 (0.2)
Lateral mobilization of prosthesis	5 (1.1)
Capsular contracture	33 (7.48)
Total	441 (100)

The NAC excision rate was 5.4% (24 cases) due to confirmed presence of cancer cells in the subareolar tissue by frozen section analysis or on final histology.

Of all patients, 83 (18.82%) were smokers, 27 (6.1%) had diabetes mellitus (DM), and 29 (6.6%) had a body mass index (BMI) of $>30 \text{ kg/m}^2$.

Early and late postoperative complications were noted in 64 (14.51%) procedures (table 3). The most common complication was skin flap ischemia/necrosis (26 patients, 5.2%). Most ischemic complications were treated conservatively (22/26), while 4 cases required surgical excision of the necrotic skin with primary suturing

and, in 1 case, with latissimus dorsi flap reconstruction. In the peri-operative period, only 1 (0.2%) case experienced NAC necrosis.

Delayed oncological treatment (which started between 6 and 12 weeks after NSM) due to early surgical complications occurred in only 11 (2.5%) patients.

Capsular contracture, as a late complication, occurred in 33 (7.48%) cases. All of these patients had irradiation as part of their adjuvant treatment. The severity of capsular contracture was estimated according to the Baker classification (10 cases grade II, 15 grade III, and 8 cases grade IV). 16 patients underwent capsulotomy with re-implantation of the prosthesis.

Prosthesis explantation due to complications was necessary in 11 (2.5%) cases; the main reason was infection (9 cases), and 2 patients expressed the wish to have the silicone implant removed due to chronic chest pain and discomfort. In 15 cases, prosthesis explantation was needed due to local recurrence requiring mastectomy.

Neoadjuvant chemotherapy, implant size $>500 \text{ ml}$, DM, BMI $> 25 \text{ kg/m}^2$, and incisions other than lateral were risk factors for early complications ($p < 0.001$). Smoking and irradiation (patients with previous BCS) had no impact on the early surgical complication rate.

During follow-up, local relapse occurred in 32 (7.3%) patients, with 3 cases in stage I, 10 cases in stage II, and 19 cases in stage III and a mean time to recurrence of 21 months. 2 recurrences were in the NAC. Distant metastases were diagnosed in 68 (15.6%) patients, and 53 (12.2%) patients died during the follow-up period (fig. 1).

Discussion

In 1962, Freeman [11] first reported the technique of subcutaneous mastectomy followed by reconstruction. Techniques have evolved since that time and today comprise the use of prosthetic materials, autologous tissue, or a combination thereof [12]. The cosmetic outcome of reconstruction with implant after postoperative radiotherapy is not always satisfactory because of capsular contracture and skin changes due to irradiation [13]. For that reason, Petit et al. [14] suggested the concept of NSM followed by intraoperative radiotherapy and immediate reconstruction. Some authors consider autologous reconstruction to be the best option due to better esthetic result compared to implant reconstructions [15]. The latissimus dorsi myocutaneous flap was the method of choice for autologous tissue breast reconstruction until the introduction of the transverse rectus abdominis musculocutaneous (TRAM) flap in 1982 [16]. The advantage of the TRAM flap is the provision of an adequate soft tissue bulk to produce a satisfactory breast shape and yield a permanent lifelong result. Many other flaps and techniques can be used in primary and secondary autologous breast reconstructions, but most of them are demanding on both the patient and the surgeon [12]. Therefore, subpectoral implantation of silicone prostheses after NSM has become a widely used method for breast reconstruction, and compared to autologous tissue reconstructions it is a technically less demanding procedure with shorter operating, hospitalization, and recovery times [17].

Surgical Complications

The surgical outcome of NSM is not always predictable. Concerns are mostly related to increased early postoperative complications such as infection, wound healing problems, and ischemia or necrosis of the skin or NAC [18–20]. Age, skin incision, flap thickness, reconstruction type, smoking, neoadjuvant chemotherapy, preoperative irradiation, and comorbidities have been reported as risk factors for ischemic complications concerning the skin and NAC [1–4, 18, 19, 21–26]. Patients with an increased BMI and DM are likely to have additional complications due to associated vascular disease [25].

Neoadjuvant chemotherapy is gaining acceptance as an option for locally advanced breast cancer treatment but was found to be a risk factor for early surgical complications in our study. However, other authors did not confirm a relationship between neoadjuvant chemotherapy and surgical complications [27, 28].

The rate of NAC and breast skin necrosis is usually less than 10% [19, 21]. We identified 26 (5.90%) patients with necrotic complications with only 1 (0.2%) NAC necrosis. Komorowski et al. [19] in their analysis of 38 NSM had 15.8% necrotic complications, and only age >45 years had a statistical impact on skin necrosis. They used a periareolar omega-shaped approach in 79% of cases. In our study, incisions other than lateral were a risk factor for skin ischemia/necrosis. We believe that periareolar incisions might compromise the blood supply and thus prefer lateral incisions as was also suggested by some other authors [29, 30]. After removal of the

glandular breast tissue under the dermis, the NAC and the skin are poorly vascularized by the dermal vessel network. Nipple microvessels and their position to the lactiferous ducts were thoroughly analyzed by Rusby et al. [31]. The mean duct bundle diameter in microscopic sections was 5.2 mm. According to their study, in a non-irradiated nipple, leaving a 2-mm rim of peripheral nipple tissue retains 50% of the vessels of the nipple cross section with complete excision of the duct bundle in 96% of cases, while a thicker peripheral rim of 3 mm retains 66% of vessels but with complete duct excision in 87% cases. This study shows that the surgeon is forced to make a compromise between removal of all duct tissue and the preservation of blood vessels to maintain the viability of the nipple remnant. In our study, breast irradiation (in patients with previous BCS) was not associated with skin ischemic complications.

Capsular contracture is the most frequent late complication and a major cause of poor cosmetic outcome. We observed a capsular contracture rate of 7.48%, similar to other series [32, 33]. In a study by Contant et al. [34], capsular contracture was seen significantly more often around prostheses implanted in a previously irradiated area ($p < 0.0005$), and irradiation after NSM was associated with a significant increase in capsular contracture ($p = 0.001$). Pinsolle et al. [35] also confirmed an impact of radiotherapy on the capsular contracture rate. A number of studies suggested that hematoma and peri-prosthetic bacterial contamination may also be associated with a higher incidence of capsular contracture [36–39].

An explantation rate due to complications of only 2.5% in our study and delayed oncological treatment due to complications in 2.5% of patients suggests the safety of the procedure.

Oncological Safety of NSM

The NAC excision rate in our study was 5.4% (24 cases) due to confirmed presence of cancer cells in subareolar tissue by frozen section analysis or on final histology. Histological studies showed that nipple involvement ranges from 5% to as much as 58% depending on the size of the primary breast tumor, location, multicentricity, lymph node positivity, and presence of an extensive intraductal component [40–42]. Gulben et al. [41], in a multivariate logistic regression analysis, showed that tumor location (central vs. peripheral; $p < 0.0001$), number of positive axillary lymph nodes (≥ 10 vs. < 10 ; $p < 0.005$), and lymphatic vascular invasion (yes vs. no; $p < 0.0001$) were the most important prognostic factors for NAC involvement and that patients with 2 or 3 risk factors should be considered at high risk for cancer involvement of the NAC.

In our series, 121 (27.8%) patients had stage III breast cancer. NSM in locally advanced breast cancer is not contraindicated if surgery is radical and adjuvant treatment starts in time. Although patients with locally advanced disease have a poorer prognosis, they deserve to be given the same treatment options as early-stage patients. Avoiding immediate reconstructive methods in this group of patients merely for economic reasons is not justified. In a study of 146 women with primary reconstruction, the risks of distant metastasis and breast cancer-related death were signifi-

cantly lower in the breast reconstruction group than in the control group treated with mastectomy. The risks of local recurrence, second breast cancers, and second primary cancers at a site other than the breast were not significantly different between the 2 groups [43]. In the report by Spiegel et al. [44] with a mean follow-up of 9.8 years in 221 patients after SSM with immediate reconstructions, the incidence of local recurrence was 5.6% for invasive cancer and 0% for DCIS. The metastatic recurrence rate in the invasive carcinoma group was 6.8%. In this cohort, local recurrence appeared in 7.3% of patients, mostly with stage III cases. Hence, according to our results and those of other authors, the risk of local recurrence in NSM is even lower than in BCS, confirming the oncological safety of NSM with primary reconstruction [9, 45, 46].

Conclusion

Based on well-planned surgical technique, NSM with primary implant reconstruction is an oncologically and surgically appropriate treatment for most women requiring mastectomy. Risk factors for surgical complications and NAC involvement have to be carefully discussed preoperatively by a multidisciplinary team. The patient has to understand the risks related to the procedure, especially in terms of immediate surgical complications, esthetic outcome, and the possible need for revisional surgery.

Disclosure Statement

The authors declare that they have no competing interests.

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