Evaluation of Local Oncologic Safety in Nipple–Areola Complex-sparing Mastectomy After Primary Chemotherapy: A Propensity Score-matched Study

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Abstract

After primary chemotherapy, large operable T2-T3 breast cancers might be suitable for nipple–areolar complex-sparing mastectomy (NSM). Using propensity score analysis, NSM did not show an increased risk of local recurrence compared with conventional mastectomy. The risk of local recurrence was associated with the stage of disease before primary chemotherapy.

Background: Nipple–areola complex-sparing mastectomy (NSM), extending the concept of skin-sparing mastectomy, allows for the provision of a better cosmetic result. Large operable T2-T3 breast cancer might theoretically appear suitable for this surgical option as an alternative to conventional mastectomy or breast-conserving surgery, when a good response to primary chemotherapy has been achieved. **Patients and Methods:** From January 2009 to May 2013, 422 patients with invasive breast cancer were progressively accrued to NSM. Of the 422 patients, 361 underwent NSM as first-line treatment (NSM group), and 61 underwent surgery after primary chemotherapy (NSM-PC group). A total of 151 breast cancer patients, who had undergone PC and conventional total mastectomy (TM-PC group) from 2004 to 2009 were evaluated as comparative group with respect to the NSM-PC group. Using propensity score matching, local disease-free survival (LDFS) was evaluated comparatively. **Results:** The rate of nipple–areola involvement in the NSM and NSM-PC groups was 13.3% and 9.8%, respectively ($P = .539$). The nipple–areola involvement in the NSM and NSM-PC groups was significantly associated with the tumor size (odds ratio [OR], 1.48; 95% confidence interval [CI], 1.13-1.95; $P = .004$), plurifocal or pluricentric tumor (OR, 3.18; 95% CI, 1.72-5.89; $P < .001$), and the presence of an intraductal component (OR, 2.38; 95% CI, 1.22-4.64; $P = .011$). The LDFS in the NSM-PC and TM-PC matched cohorts did not show a significant difference, with a 4-year LDFS of 0.89 (95% CI, 0.77-0.95) and 0.93 (95% CI, 0.83-0.97), respectively (hazard ratio [HR], 1.31; 95% CI, 0.40-4.35; $P = .655$). The NSM-PC cohort was also compared with the NSM cohort in terms of LDFS using 2 different matching criteria, with the tumor size before and after neoadjuvant chemotherapy as the balancing covariate. In the first of the 2 comparisons, the hazards of local relapse were comparable between the 2 matched groups (HR, 1.23; 95% CI, 0.37-4.04; $P = .739$). In the second comparison, the NSM-PC patients showed a significant greater hazard of local relapse than did the NSM patients (HR, 3.60; 95% CI, 1.10-11.80; $P = .035$). **Conclusion:** NSM might be a valuable option for large breast cancer treated by primary chemotherapy. The rate of local relapse seemed to be related to the disease stage, and no significant association with the type of surgery was detected.

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Introduction

Since the Halstedian design of mastectomy with its concept of radicality and all the conceptual changes in breast cancer management that have led to conservative surgery,[1,2] nipple–areola complex-sparing mastectomy (NSM) remains a current challenge to obtain the best oncologic and cosmetic results when conservative surgery is not possible. The intrinsic limits to breast conservative surgery consist of the tumor size, site, ratio between the primary tumor volume and mammary gland, extension of intraductal disease, multicentric invasive cancer and, finally, the will, information, and preference of patients.[3,4]

NSM is a more recent surgical procedure that has further extended the concept of skin-sparing mastectomy,[5,6] leaving intact the nipple–areola complex and providing a better cosmetic result. It has also been defined as "conservative mastectomy."[7]

Just as with skin-sparing mastectomy,[8-10] concerns have been raised about the correct clinical indications, surgical technique, and greater risk of local recurrence resulting from less resection of skin and preservation of the nipple–areola complex compared with conventional mastectomy.[4,10-13] Furthermore, several studies have investigated the clinical and biologic factors that are predictive of nipple involvement to aid in patient selection for NSM.[14-16]

To date, NSM has generally been indicated for prophylactic mastectomy in BRCA mutation carriers or extensive intraductal carcinoma with or without small multicentric invasive carcinoma in properly selected patients.[17-20] However, in some studies, the indication for NSM has been broadened to larger tumors.[21,22]

Large, operable T2-T3 breast cancer that has undergone primary chemotherapy (PC) might theoretically appear suitable for NSM. This surgical option could be an alternative to conventional total mastectomy and breast-conserving surgery in cases of unfavorable breast size with a good response to PC.

In the present study, the data from a series of consecutive breast cancer patients treated with this sequential therapeutic strategy (PC followed by NSM [NSM-PC group]) were analyzed to evaluate the feasibility and local oncologic safety of NSM after PC. We considered the evaluation of nipple–areola involvement at surgery mandatory in terms of feasibility and safety. The risk of local recurrence was assessed using propensity score analysis with 2 different groups of patients. The first group was a consecutive series of breast cancer patients treated with NSM as primary treatment (NSM group). The second group was a previous consecutive series of breast cancer patients treated with PC and conventional total mastectomy (TM-PC group).

Patients and Methods

Our institutional review board and ethics committee approved the present study (approval no. INT177/13) and was recorded in Clinicaltrials.gov (ClinicalTrials.gov identifier, NCT02471742). All the study patients were treated in our institute.

Patient Selection for Neoadjuvant Chemotherapy

Both groups of patients treated with PC (NSM-PC and TM-PC) had stage T2-T3N0-N1 breast cancer. The exclusion criteria for the present study were patients with progressive disease during chemotherapy, synchronous distant metastases, or other clinical diseases (eg, cardiovascular diseases) that affected the optimal therapeutic strategy. For both groups undergoing PC and mastectomy, with or without sparing of the nipple–areola complex, the clinical and pathologic characteristics at biopsy and before the beginning of chemotherapy showed no significant differences considering age, site of tumor inside the breast, TNM classification, tumor size, grade, or estrogen receptor, progesterone receptor, or HER2 expression.

Patient Selection for NSM

In our series of NSM patients, with or without PC, the selection of patients for sparing of the nipple–areola complex was based on the following criteria: tumor nodule without adherence to the skin, no nipple retraction, and retroareolar main ducts free of neoplastic tissue at frozen section examination. Furthermore, patients were considered eligible for NSM even if the tumor was in close proximity (< 1 cm) to the nipple–areola complex on physical and radiologic examination. The exclusion criteria were nipple retraction, Paget's disease, inflammatory changes of the breast, and bloody discharge from the nipple.

The women who underwent NSM as primary therapy (NSM group) all had T1-T3N0-N1M0 breast cancer.

NSM Technique

NSM was performed using a radial "italic S-like" incision in the equatorial/upper external site of the breast in all women with small or medium breasts (A-C breast cup size). In particular, in a very small number of cases with large breasts (D or DD breast cup size) and severe ptosis, the oncoplastic technique of skin-reducing mastectomy,[23] with a T-inverted pattern was planned to preserve nipple–areola complex vitality. Mastectomy was performed by leaving a skin layer with an approximate thickness of 1 to 2 mm, preserving the essential capillaries supplying the skin. If oncologic safety allowed, careful preservation of the fascia of the major pectoral muscle extended at the inframammary and parasternal folds was performed to allow for better reconstruction. Particular attention was given to dissect the areola away from the underlying tissue, even if a thin disc of gland tissue remained under the areola. When the tissue containing the main ducts under the nipple was evident, the nipple was inverted to ease complete removal of this tissue, which was then sent for frozen section examination.

Reconstructive Technique

The reconstructive procedures consisted of 2-stage versus 1-stage reconstruction. The 2-stage procedure included planned submuscular insertion (under the pectoralis major and serratus anterior) of a saline anatomic expander, followed by substitution with a permanent silicone implant. One-stage reconstruction mainly included the insertion of a silicone implant into a dual-plane pocket,[24] except for in a few cases in which a synthetic mesh or an acellular dermal matrix was used to close the lower pocket.

Pathologic Evaluation of Tissue Inside the Nipple

Tissue samples for frozen section analysis were taken from the base of the nipple–areola complex and were stained with hematoxylin and eosin. The presence of invasive breast cancer or ductal carcinoma in situ component (DCIS) in the main ducts of the