Doctor of Philosophy

Analysis of Risk Factors Associated with Recurrence at the Nipple-areola Complex Following Nipple-sparing Mastectomy and Immediate Breast Reconstruction for Breast Cancer

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Abstract

Background: Nipple-sparing mastectomy (NSM) has become increasingly prevalent in patients with breast cancer who requiring mastectomy. However, there are little data regarding long-term oncologic outcomes following therapeutic NSM. The main concern associated with NSM is the risk of local recurrence at the retained nipple-areola complex (NAC) consequent to occult nipple involvement. In this study, we evaluated the NAC recurrence (NR) rate of patients with breast cancer who underwent NSM followed by immediate breast reconstruction and investigated potential risk factors for NR.

Patients and Methods: A retrospective chart review was performed in 1,161 consecutive patients with invasive breast cancer (group A, n=962) and pure ductal carcinoma in situ (group B, n=199) who underwent NSM and immediate breast reconstruction between March 2003 and December 2015 at the Asan Medical Center (Seoul, Korea). Risk factors for NR were analyzed using univariate (chi-square test) and multivariate (Cox model) methods.

Results: The median follow-up duration after surgery were 85 (range, 14–185) months for group A and 97 (range, 39–186) months for group B. In group A, 39 cases (4.1%) involved NR as the first event; In group B, 6 cases (3.0%) involved NR as the first event. The 5-year cumulative incidence of NR were 3.5% for group A, and 2.5% for group B. In group A, the significant risk factors for NR were multifocal/multicentric disease, negative hormone receptor (HR)/positive human epidermal growth factor receptor 2 (HER2) subtype, high histologic grade, and extensive intraductal component (EIC). In group B, the risk factors for NR were high nuclear grade, negative receptor status, HER2 positivity, and HR-/HER2+ subtype. All 45 NR cases involved wide local excision. In group A, patients with and without NR as the first event did not differ significantly in distant metastasis-free survival (p=0.949) or overall survival (p=0.211).

Conclusion: The patients had a low incidence of NR after NSM and immediate breast reconstruction in current setting. Biological factors of tumor should be considered before determining the NSM procedure.

Key words: Breast cancer, Nipple-sparing mastectomy, Nipple-areola complex recurrence, Risk factor

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Introduction

The surgical management of breast cancer has dramatically evolved over the past decades. Breast-conserving surgery (BCS) has replaced the radical treatment approaches and is now an established standard of care. However, approximately one-third of patients with breast cancer still require mastectomy.[1] Recently, there is evidence that the mastectomy rate is increasing.[1,2] This reversing trend is related to the growing preference for breast reconstruction and contralateral prophylactic mastectomy, as well as the paradigm shift in mastectomy patterns.[2,3,4]

Nipple-sparing mastectomy (NSM), which evolved from skin-sparing mastectomy (SSM), is a leap forward in breast-conserving techniques in that the nipple-areola complex is preserved along with the skin envelope at the time of mastectomy. Multiple prospective and retrospective studies on NSM have demonstrated the oncological and surgical safety of this technique, as well as the superior aesthetic outcomes and improved quality of life achieved when it is combined with immediate breast reconstruction.[5-7] Nevertheless, the application of NSM in breast cancer remains controversial because of the limited available data, including long-term follow-up data, from accurate evaluations of modern therapeutic NSM. Currently, the main concern associated with NSM is the risk of local recurrence at the retained NAC consequent to occult nipple involvement. As increasing numbers of patients with breast cancer are selecting NSM,[8] it is important to identify the incidence of NAC recurrence (NR) after NSM, describe the associated risk factors. Previous studies have reported NR incidence rates of 0–3.7% after NSM.[9-17] However, most of these series included heterogeneous populations, as well as relatively short follow-up durations. The current study, which included long-term follow-up, aimed to assess the incidence and risk factors associated with NR in a large series of patients with invasive breast cancer and ductal carcinoma in situ

(DCIS) who underwent NSM and immediate breast reconstruction at a single institution.

Patients and Methods

1. *Study Population*

From March 2003 to December 2015, 19,964 patients with breast cancer underwent surgical treatment at the Asan Medical Center (Seoul, Korea). Of these, we retrospectively analyzed 1,161 patients with breast cancer who underwent NSM and immediate breast reconstruction: 962 patients with invasive breast cancer (group A) and 199 patients with DCIS (group B). Patients who underwent neoadjuvant systemic therapy or palliative surgery were excluded from this study. The study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2018-1579). Because of the retrospective nature of the study, the requirement for informed consent was waived.

2. *Indications and surgical technique for NSM*

Our indications for NSM were any stage, tumor size, and tumor-to-nipple distance with indications for mastectomy. Patients with a clinically normal NAC and no skin involvement were offered the option of NSM. NSM was performed as previously described in our study.[5] In all cases, a retroareolar frozen section was collected and examined intraoperatively. The subdermal glandular tissue was undermined in the retroareolar area, leaving 1–2 mm of intact dermis. Next, a thin layer of glandular tissue was collected under the areola for frozen sectioning (**Figure 1**). The NAC was preserved if the shape, color, and palpated features of the nipple were normal and when the retroareolar ducts were confirmed to be tumor-free in intraoperatively collected frozen biopsies. In case the retroareolar ducts were positive for malignancy at the intraoperative frozen section, nipple with or without areola was removed immediately and the surgical procedure was converted to SSM. If the retroareolar tissue was positive for malignancy at the final pathology, nipple with or without areola was also

removed in these cases and excluded from the NSM cohort. In our center, sentinel lymph node biopsy (SLNB) was performed for all patients who underwent mastectomy for DCIS in principle. However, in a small proportion of patients in group B (8.5%), SLNB was not performed either at the discretion of the treating surgeon or due to the patients had previously received BCS for DCIS. Sentinel lymph node biopsy and/or axillary lymph node dissection were performed in all patients in group A. All patients underwent immediate breast reconstruction via autologous or prosthetic methods by plastic surgeons. Adjuvant systemic treatment was performed according to the contemporary recommendations of the St. Gallen Consensus Conference[18] and NCCN guidelines.[19]

3. Characteristics

Clinicopathological, treatment, and follow-up data were obtained from the the prospectively maintained database of the Asan Medical Center–Breast Cancer Center (AMC-BCC). In group A, the age at diagnosis, type of surgery, type of adjuvant systemic treatment, tumor stage, number of positive lymph node, histologic grade, multifocality/multicentricity, lymphovascular invasion (LVI), molecular subtype, tumor-nipple distance (TND), extensive intraductal component (EIC), and tumor histological type were carefully reviewed. EIC was considered positive when it comprised more than 20% of the tumor size. Tumor staging were conducted according to the 7th American Joint Committee on Cancer Staging Manual.[20] In group B, the age at diagnosis, tumor size, TND, multifocality/multicentricity, nuclear grade, comedonecrosis, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, and surgical margin status were carefully reviewed. Hormone receptor (HR) positivity was defined as ER+ and/or PR+. Molecular subtype was defined as followings: HR+/HER2- (ER or PR+ and HER2-), HR+/HER2+ (ER+ or PR+ and HER2+), HR-/HER2+ (ER-, PR- and HER2+), and triple negative (ER-,

PR- and HER2-). A positive surgical margin was defined as tumor touching ink in the mastectomy specimen. TND was determined as the shortest distance between the tumor and nipple base on magnetic resonance imaging, ultrasonography, or mammography. In cases of multifocal/multicentric diseases, the closest lesion to the nipple was used for distance calculation.

4. Follow-up

Postoperatively, the patients were regularly followed every 3-6 months for the first 5 years and annually thereafter. Recurrence and metastasis were identified based on the results of clinical examination, mammography, chest radiography, and tumor marker (CA15–3) measurements, which were performed every follow-up visit. Abnormal clinical findings may have been evaluated through further studies, including chest computed tomography, bone scan, and liver ultrasonography. Punch needle or incisional biopsy was performed to evaluate suspected lesions in the NAC, and NR was defined as a biopsy-proven cancer in the NAC tissue. Patients who failed to present for examination were contacted via telephone to confirm that they remained alive.

5. Statistical analysis

The primary endpoint was NR as the first event. Patients with initial recurrences at other sites were excluded from the NR group. The time to recurrence or metastasis was measured from the date of surgery until occurrence of the event. Distant metastasis-free survival (DMFS) was defined as the interval from the date of surgery to the first occurrence of distant metastasis, while overall survival (OS) was defined as the interval from the date of surgery to death. For univariate analysis of risk factors associated with NR, the chi-square test was used to compare differences between subgroups. For multivariate analysis, a Cox proportional

hazard regression model was used to analyze the relationship between clinicopathological variables and NR and identify the potential risk factors for NR after NSM. To evaluate the impact of NR on prognosis, the DMFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed using IBM SPSS Statistics version 24.0 for Windows (IBM Corp., Armonk, NY, USA). A P-value <0.05 indicated statistical significance.

Results

1. Patient, tumor and treatment characteristics

Patient, tumor, and treatment characteristics of the patients are shown in **Table 1** (group A) and **Table 2** (group B). The median age at diagnosis for entire cohort was 43 years (range, 20–67 years). The median TND were 2.0cm (0.1-10.0cm) in group A and 2.0cm (0.5-6.4cm) in group B. In the entire cohort, we confirmed that the pathological diagnoses of both frozen and permanent biopsy sections revealed no evidence of tumor involvement at the retroareolar resection margin. A total of 874 patients (75.3%) underwent autologous flap reconstruction, and 287 (24.7%) had reconstruction with an implant or tissue expander. In group A, 508 patients (52.8%) were treated with adjuvant chemotherapy, and 729 (75.8%) were treated with adjuvant hormonal therapy. Ninety-seven patients (10.1%) received adjuvant radiotherapy. In group B, sentinel lymph node biopsy was performed in 182 patients (91.5%); none (0%) were positive on frozen section biopsy. Adjuvant hormonal therapy was administered to 15 patients (7.5%) after the initial surgery, and no adjuvant radiotherapy was performed before locoregional recurrence in group B.

2. NR

The median follow-up duration after surgery were 85 (range, 14–185) months for group A and 97 (range, 39–186) months for group B. In group A, 39 cases (4.1%) involved NR as the first event; these excluded NRs diagnosed after a locoregional recurrence or distant metastases. In addition, 42 cases (4.4%) involved local recurrence in the skin or chest wall outside of the NAC as the first event. Four cases involved concurrent recurrence at the NAC and skin or chest wall. The 5-year cumulative incidence of NR was 3.5% (n=34), and the 5-year cumulative incidence of overall local recurrence was 6.7% in group A. The median time interval from surgery to NR

was 35 months (range, 7–135 months) in group A. In group B, 6 cases (3.0%) involved NR as the first event. In addition, 3 cases (1.5%) involved local recurrence in the chest wall. The 5-year cumulative incidence of NR was 2.5% (n=5), and the 5-year cumulative incidence of overall local recurrence was 3.5% in group B. The median time interval from surgery to NR was 39 months (range, 23–94 months) in group B. The characteristics of the 45 patients with NR are described in **Table 3**. Among the 45 NRs, the recurrent tumor histology was invasive carcinoma in 16 patients (35.6%), Paget disease with/without DCIS in 21 patients (46.7%), DCIS in 7 patients (15.6%), and Paget disease with microinvasive ductal carcinoma in 1 patient (2.2%).

3. Risk factors for NR

In group A, the univariate analyses identified associations of multifocality/multicentricity, molecular subtype, histologic grade, and EIC with NR (**Table 4**). Of these, multifocality/multicentricity (hazard ratio [HR]=3.309; 95% confidence interval [CI], 1.501–7.294; p=0.003), hormone receptor (HR)(-)/human epidermal growth factor receptor 2 (HER-2)(+) subtype (HR=3.051; 95% CI, 1.194–7.796; p=0.020), high histologic grade (HR=2.641; 95% CI, 1.132–6.160; p=0.025), and presence of EIC (HR=3.338; 95% CI, 1.262–8.824; p=0.015) were independent risk factors for NR in a multivariate analysis (**Table 5**). In group B, high nuclear grade, negative receptor status, HER2 positivity, and HR-/HER2+ subtype were significant risk factors for NR in univariate analysis (**Table 6**). Multivariate analysis was not carried out for NR due to the paucity of events.

4. Treatment and prognosis of patients with NR

All 45 patients with NR underwent wide local excision. Patients with NR had a mean follow-up duration of 55 months (range, 5–121 months) after NAC removal, during which 3 patients

(6.7%) developed distant metastasis within 5, 24, and 56 months, respectively. All patients who had NR were confirmed alive at the last follow-up, except one patient in group B who presented with concurrent NR and bilateral axillary lymph node metastases died due to the subsequent lung and brain metastases. In group A, the 10-year DMFS rates were 89.3% and 94.3% in patients with and without NR, respectively; the 10-year OS rates were 100% and 94.5% in patients with and without NR, respectively. A Kaplan–Meier survival analysis found no significant differences in DMFS (log-rank test, p=0.949, **Figure 2A**) and OS (log-rank test, p=0.211, **Figure 2B**) between patients who had and those who did not have NR as the first event. The 10-year OS for group B was 98.5%.

Discussion

NSM followed by immediate breast reconstruction for the surgical treatment of breast cancer has gained increased acceptance, with a growing emphasis on the achievement of excellent aesthetic results and improved quality of life without compromising oncologic safety. However, limited long-term follow-up data are available regarding the oncologic safety of modern NSM in terms of NR and survival. To our knowledge, the current study is the first to focus specifically on the incidence and risk factors of NR as the first event after NSM in a large series of patients with invasive breast cancer and ductal carcinoma in situ in a long-term follow-up period. We also examined treatments and outcomes following NR after NSM. Although published studies have demonstrated low rates of NR (0–3.7%) after NSM,[9-17] these findings were observed in a heterogeneous group of patients and reported in variable follow-up durations. In a series by Jensen et al.,[21] no cases of NR were reported among 149 NSMs in a mean follow-up duration of 60.2 months; however, 57% of these cases did not involve invasive cancer.[21] In a study by Wang et al.,[22] no cases of NR were reported among 981 NSMs; however, the follow-up evaluation was limited to 29 months, and 52% of the surgeries were performed prophylactically or for in situ disease.[22] During a median follow-up duration of 78 months, Sakurai et al. reported an NR rate of 3.7% in 788 cases of NSMs without radiotherapy between 1985 and 2004.[12] A few other NSM series that reported follow-up durations of >5 years involved patients treated in the 1980s and/or 1990s,[23-25] when the adjuvant systemic therapy and radiation therapy regimens currently used in clinics had not yet been established as the gold standard. Furthermore, We found only two studies focused on NSM for DCIS; however, these had an insufficient number of patients.[26,27] In 2018, Lago et al. reported 69 patients with DCIS who underwent NSM.[26] With a mean follow-up of 142.6 ± 70.7 months, they demonstrated a local recurrence rate of 11.6%, which was higher than our

series. However, in contrast to our series, they included patients with recurrent breast cancer after breast-conserving therapy and patients treated in the 1980s and 1990s. Although no frozen section examination of the retroareolar margin was performed in their cohort, only one case (1.4%) of Paget's NR was observed.[26] Leclère et al. reported another NSM series of 41 patients with DCIS.[27] However, long-term follow-up data were available in only 19 patients (46%). For these 19 patients, the local recurrence rate was 5.3% during a mean follow-up time of 7.1 ± 2.9 years. The only patient who experienced a recurrence was a Paget's disease recurrence in the NAC and skin 3.7 years after NSM.[27] In our study, we included patients with invasive carcinoma and DCIS who underwent NSM and immediate breast reconstruction between 2003 and 2015 and identified a overall NR incidence of 3.9% (4.1% for group A and 3.0% for group B), which is low. The 5-year cumulative incidence of NR were 3.5% for group A, and 2.5% for group B. This result is acceptable, given the study population in the current series and the relatively long follow-up period.

Identifying the clinicopathological features of patients with a high risk of recurrence is important when considering patient selection, treatment, and surveillance. Previously, only three studies had analyzed the risk factors associated with NR after NSM; of these, two involved only univariate analyses because of the small number of events.[13,14,28] Only one study investigated variables through a multivariate analysis. In the study on 934 NSMs for invasive and intraepithelial breast cancer with a follow-up duration of 50 months, including 11 cases of NR, Petit et al.[14] determined that the tumor size, receptor status, HER2/neu status, grade, and Ki-67 proliferation index were associated with the risk of NR in a multivariate analysis.[14] Regarding the operative technique for NSM, Petit et al. described leaving a 5-mm-thick layer of glandular tissue beneath the NAC to avoid flap necrosis and the intraoperative delivery of electron-beam radiotherapy exclusively to the NAC to minimize the risk of local recurrence. This technique differed significantly from the protocol used at our institution;

therefore, the outcomes may not be applicable to our series. In another study from the same institution of Petit et al.,[14] Lohsiriwat et al.[28] reported seven cases involving local recurrence of Paget disease after NSM. In that study, univariate analyses identified primary carcinoma with ductal intraepithelial neoplasia or IDC with EIC, negative hormonal receptor status, high pathologic grade, HER2/neu overexpression, and HER2 positivity as risk factors for local recurrence of Paget disease.[28] Shimo et al.[13] found that young age, estrogen receptor negativity, HER2 overexpression, and HER2-enriched subtype were significantly associated with a higher rate of recurrence at the NAC in a univariate analysis.[13] In our study, a multivariate analysis identified associations of multifocality/multicentricity, HR-/HER2+ subtype, high histologic grade, and presence of EIC with an increased risk of NR after NSM for invasive cancer. While high nuclear grade, negative receptor status, HER2 positivity, and HR-/HER2+ subtype were associated with increased risk of NR in DCIS. However, we did not find statistically significant correlations between TND and NR.

The major oncological concern typically associated with NSM is the risk of local recurrence at the retained NAC consequent to occult nipple involvement. Numerous studies have reported that a short TND is a significant predictor for nipple involvement.[29,30] Traditionally, varied TND cutoffs of 1 or 2 cm have been recommended by different institutions for the selection of appropriate NSM candidates;[11,27,31,32] however, controversy remains. In the current study, we specifically examined the association between TND and NR after NSM. There was no statistically significant difference in the NR rate when patients were stratified by TND using a cutoff of 1 cm.

Although the criteria used to select NSM for breast cancer treatment have broadened over time,[33] consensus has not yet been reached regarding this issue. The traditional guidelines were based on studies recommending the selection of patients with the lowest risk of NAC involvement. The predictors reported to be associated with occult NAC involvement include

tumor size, TND, HER2 amplification, LVI, EIC, multifocal disease, and axillary lymph nodal metastasis.[29,30,34,35] Our indications for NSM were any stage, tumor size, and TND. Furthermore, we routinely performed intraoperative frozen biopsy examinations of the retroareolar resection margins to determine occult nipple involvement. The NAC was preserved if the palpation findings, shape, and color of the nipple were normal and the NAC ducts were confirmed to be tumor-free in intraoperatively collected frozen biopsies. Our results confirm the validity of our indications for NSM and an acceptably low incidence of NR.

The prognostic significance of molecular biomarkers of DCIS, such as ER, PR, and HER2 status, and the subtypes classified by grouping these receptors remain controversial. Williams et al.[36] reported that Luminal B, HER2 type, and triple negative DCIS were associated with increased risk of both overall and invasive recurrence compared with Luminal A DCIS.[36] Another study by Rakovitch et al.[37] reported that HER2/neu+ and Ki67+ DCIS have a higher risk of noninvasive local recurrence after BCS.[37] In contrast, other researchers found a lack of significant association between various biomarkers and risk of recurrence.[38-40] In our study, ER negativity, PR negativity, HER2 positivity, and HR-/HER2+ subtype were associated with increased risk of NR in univariate analysis. The number of patients and NR events in group B may still be too low to make definitive statements regarding risk factors for recurrence with strong statistical power; however, our results suggest that determining the molecular subtype of DCIS might be helpful in identifying patients with high risk of recurrence and guiding patient management. Further research in other large cohorts is needed to validate our results.

Notably, six of 9 local recurrences in group B presented as NR in current study. This result show that NR can occur in a significant proportion of patients with local recurrence after NSM for DCIS. We also found that presence of extensive intraductal component (EIC) independently increase the risk of NR in group A. Petit et al.[14] reported that presence of in

situ lesion or invasive carcinoma with EIC has tendency to develop a NR after NSM.[14] These results suggest that the DCIS itself seems to be associated with increased risk of NR. Accordingly, surgeons should be cautious with the possibility of NR after NSM in this patient population.

The current study presents our experience with the treatment and outcomes of patients with NR after NSM. All patients with NR underwent wide local excision, and more than half received multimodal adjuvant treatment according to the biological disease features, including hormonal therapy, chemotherapy, and/or radiotherapy. Of the 45 patients with NR as the first event in the current series, three developed distant metastases during the follow-up period; however, 44 patients survived at the last follow-up and only one patient with NR died due to the disease progression. These results indicate that the occurrence of NR has no direct significant negative impact on prognosis.

The main limitation of present study was that it involved retrospective analysis from a single institution, although from a prospectively maintained database, and may include bias. Another limitation of this study was that the BRCA1/2 mutation data were not include for risk factor analysis, which could influence the recurrence.

Conclusions

We demonstrated an acceptably low incidence of NR during the long-term follow-up in our series of patients with breast cancer who were treated with NSM and immediate breast reconstruction. We found multifocal/multicentric disease, HR-/HER2+ subtype, high histologic grade, and positive EIC were independent risk factors for NR in patients with invasive breast cancer and high nuclear grade, negative receptor status, positive HER2 status, and HR-/HER2+ subtype were associated with increased risk of NR in patients with DCIS. Accordingly, these factors should be considered when planning for NSM. The majority of patients with NR had a favorable prognosis after receiving appropriate comprehensive treatment. As more patients with breast cancer undergo NSM, our report and long-term follow-up data may be useful in providing a valid estimate of the NR prognosis and guiding management decisions.

References

1. Kang SY, Kim YS, Kim Z, et al. Basic findings regarding breast cancer in Korea in 2015: data from a breast cancer registry. *J Breast Cancer*. 2018;21:1-10.
2. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA. Nationwide trends in mastectomy for early-stage breast cancer. *JAMA Surg.* 2015;150(1):9-16.
3. Hong KY, Son Y, Chang H, Jin US. Trends in breast reconstruction: implications for the National Health Insurance Service. *Arch Plast Surg.* 2018;45(3):239-245.
4. Sisco M, Kyrillos AM, Lapin BR, Wang CE, Yao KA. Trends and variation in the use of nipple-sparing mastectomy for breast cancer in the United States. *Breast Cancer Res Treat.* 2016;160(1):111-120.
5. Kim HJ, Park EH, Lim WS, et al. Nipple areola skin-sparing mastectomy with immediate transverse rectus abdominis musculocutaneous flap reconstruction is an oncologically safe procedure: a single center study. *Ann Surg.* 2010;251(3):493-8.
6. Moo TA, Pinchinat T, Mays S, et al. Oncologic Outcomes After Nipple-Sparing Mastectomy. *Ann Surg Oncol.* 2016;23(10):3221-5.
7. Bailey CR, Ogbuagu O, Baltodano PA, et al. Quality-of-Life Outcomes Improve with Nipple-Sparing Mastectomy and Breast Reconstruction. *Plast Reconstr Surg.* 2017;140(2):219-226.
8. Agarwal S, Agarwal S, Neumayer L, et al. Therapeutic nipple-sparing mastectomy: trends based on a national cancer database. *Am J Surg.* 2014;208(1):93-8.
9. Frey JD, Salibian AA, Karp NS, et al. Comparing Therapeutic versus Prophylactic Nipple- Sparing Mastectomy: Does Indication Inform Oncologic and Reconstructive Outcomes? *Plast Reconstr Surg.* 2018;142(2):306-315.
10. Smith BL, Tang R, Rai U, et al. Oncologic Safety of Nipple-Sparing Mastectomy in

Women with Breast Cancer. *J Am Coll Surg.* 2017;225(3):361-365.

11. Adam H, Bygdeson M, de Boniface J. The oncological safety of nipple-sparing mastectomy - a Swedish matched cohort study. *Eur J Surg Oncol.* 2014;40(10):1209-1215.
12. Sakurai T, Zhang N, Suzuma T, et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. *Med Oncol.* 2013;30(1):481.
13. Shimo A, Tsugawa K, Tsuchiya S, et al. Oncologic outcomes and technical considerations of nipple-sparing mastectomies in breast cancer: experience of 425 cases from a single institution. *Breast Cancer.* 2016;23(6):851-860.
14. Petit JY, Veronesi U, Orecchia R, et al. Risk factors associated with recurrence after nipple-sparing mastectomy for invasive and intraepithelial neoplasia. *Ann Oncol.* 2012;23(8):2053-8.
15. Orzalesi L, Casella D, Santi C, et al. Nipple sparing mastectomy: Surgical and oncological outcomes from a national multicentric registry with 913 patients (1006 cases) over a six year period. *Breast.* 2016;25:75-81.
16. De La Cruz L, Moody AM, Tappy EE, et al. Overall Survival, Disease-Free Survival, Local Recurrence, and Nipple-Areolar Recurrence in the Setting of Nipple-Sparing Mastectomy: A Meta-Analysis and Systematic Review. *Ann Surg Oncol.* 2015;22(10):3241-9.
17. Galimberti V, Morigi C, Bagnardi V, et al. Oncological outcomes of nipple-sparing mastectomy: a single-center experience of 1989 patients. *Ann Surg Oncol*. 2018;25:3849-3857.
18. Curigliano G, Burstein HJ, Winer EP, et al; St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017. De-escalating and escalating

treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol*. 2017;28(8):1700-1712.

19. National Comprehensive Cancer Network (NCCN) Guidelines for treatment by site: breast cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. 2018.
20. Edge S, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010
21. Jensen JA, Orringer JS, Giuliano AE. Nipple-sparing mastectomy in 99 patients with a mean follow-up of 5 years. *Ann Surg Oncol.* 2011;18(6):1665-70.
22. Wang F, Peled AW, Garwood E, et al. Total skin-sparing mastectomy and immediate breast reconstruction: an evolution of technique and assessment of outcomes. *Ann Surg Oncol.* 2014;21(10):3223-30.
23. Gerber B, Krause A, Dieterich M, et al. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. *Ann Surg.* 2009;249(3):461-8.
24. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. *Eur J Surg Oncol.* 2008;34(2):143-8.
25. Horiguchi J, Iino JHY, Takei H, et al. A comparative study of subcutaneous mastectomy with radical mastectomy. *Anticancer Res.* 2001;21(4B):2963-7.\
26. Lago V, Maisto V, Gimenez-Climent J, Vila J, Vazquez C, Estevan R. Nipple-sparing mastectomy as treatment for patients with ductal carcinoma in situ: a 10-year follow-up study. *Breast J*. 2018;24:298-303.
27. Leclere FM, Panet-Spallina J, Kolb F, et al. Nipple-sparing mastectomy and immediate reconstruction in ductal carcinoma in situ: a critical assessment with 41 patients. *Aesthetic*

Plast Surg. 2014;38:338-343.

28. Lohsiriwat V, Martella S, Rietjens M, et al. Paget's disease as a local recurrence after nipple-sparing mastectomy: clinical presentation, treatment, outcome, and risk factor analysis. *Ann Surg Oncol.* 2012;19(6):1850-5.
29. Brachtel EF, Rusby JE, Michaelson JS, et al. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. *J Clin Oncol*. 2009;27:4948-4954.
30. Zhang H, Li Y, Moran MS, Haffty BG, Yang Q. Predictive factors of nipple involvement in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2015;151:239-249.
31. Petit JY, Veronesi U, Rey P, et al. Nipple-sparing mastectomy: risk of nipple-areolar recurrences in a series of 579 cases. *Breast Cancer Res Treat*. 2009;114:97-101.
32. D'Alonzo M, Martincich L, Biglia N, et al. Clinical and radiological predictors of nipple-areola complex involvement in breast cancer patients. *Eur J Cancer*. 2012;48:2311-2318.
33. Krajewski AC, Boughey JC, Degnim AC, et al. Expanded Indications and Improved Outcomes for Nipple-Sparing Mastectomy Over Time. *Ann Surg Oncol.* 2015;22(10):3317-23.
34. Byon W, Kim E, Kwon J, et al. Magnetic resonance imaging and clinicopathological factors for the detection of occult nipple involvement in breast cancer patients. *J Breast Cancer.* 2014;17(4):386-92.
35. Laronga C, Kemp B, Johnston D, et al. The incidence of occult nipple-areola complex involvement in breast cancer patients receiving a skin-sparing mastectomy. *Ann Surg Oncol.* 1999;6(6):609-13.
36. Williams KE, Barnes NL, Cramer A, et al. Molecular phenotypes of DCIS predict overall and invasive recurrence. *Ann Oncol*. 2015;26:1019-1025.

37. Rakovitch E, Nofech-Mozes S, Hanna W, et al. HER2/neu and Ki-67 expression predict non-invasive recurrence following breast-conserving therapy for ductal carcinoma in situ. *Br J Cancer*. 2012;106:1160-1165.
38. Cornfield DB, Palazzo JP, Schwartz GF, et al. The prognostic significance of multiple morphologic features and biologic markers in ductal carcinoma in situ of the breast: a study of a large cohort of patients treated with surgery alone. *Cancer*. 2004;100:2317-2327.
39. Zhang X, Dai H, Liu B, Song F, Chen K. Predictors for local invasive recurrence of ductal carcinoma in situ of the breast: a meta-analysis. *Eur J Cancer Prev*. 2016;25:19-28.
40. Poulakaki N, Makris GM, Battista MJ, et al. Hormonal receptor status, Ki-67 and HER2 expression: prognostic value in the recurrence of ductal carcinoma in situ of the breast? *Breast*. 2016;25:57-61.

국문초록

연구배경: 유방 절제술을 필요로 하는 유방암 환자에서 유두 보존 유방 절제술 (Nipple-sparing mastectomy, NSM)이 널리 보급되고 있으나, 치료목적의 NSM 후 장기 종양학적 결과에 관한 데이터는 아주 적다. NSM과 관련된 주된 관심사는 잠재적 유두 침범으로 인한 유두 유륜 복합체 (Nipple-areola complex, NAC)에서의 국소 재발 위험이 있다. 본 연구에서 저자는 NSM 및 동시 유방 재건술을 받은 유방암 환자들을 대상으로 유두 유륜 복합체에서의 재발 (NAC recurrence, NR)률과 NR에 영향을 미치는 잠재적 위험요인에 대해 고찰하고자 하였다.

환자 및 방법: 2003년 3월부터 2015년 12월 사이에 서울아산병원에서 침윤성 유방암 (A 그룹, n=962)과 순수 유방상피내암 (B 그룹, n=199) 진단을 받고 NSM 및 동시 유방 재건술을 받은 1,161 명의 환자들을 대상으로 후향적 차트 검토를 시행하였다. NR에 영향을 미치는 위험요인은 단변량 (카이-제곱 검정) 및 다변량 (Cox 모델) 분석방법을 적용하였다.

결과: 수술 후 평균 추적 기간은 A 그룹에서 85 (14-148)개월, B 그룹에서 97 (39-186)개월 이었다. 이 기간 중 A 그룹에서 39 건 (4.1%)의 NR이 첫 번째 재발로 확인되었고 B 그룹에서는 6 건 (3.0%)의 NR이 첫 번째 재발로 확인되었다. 5 년 누적 NR의 발생률은 A 그룹의 경우 3.5%, B 그룹의 경우 2.5%로 고찰되었다. A 그룹에서 NR에 영향을 미치는 위험요인으로는 다발성 (Multifocal/multicentricity) 질병, 호르몬 수용체 (Hormone receptor, HR) 음성/human epidermal growth factor receptor 2 (HER2) 양성 아형, 높은 조직학적

등급 (Histologic grade), 및 광범위한 유관 내 병변 (Extensive intraductal component, EIC) 등으로 확인되었다. B 그룹에서 NR의 위험요인으로는 높은 핵등급 (Nuclear grade), 음성 수용체 상태, HER2 양성 및 HR-/HER2+ 아형 이었다. 전체 45 건의 NR사례에서 광범위한 국소 절제술이 시행되었다. A 그룹에서 첫 재발로 NR이 발생한 환자 군과 발생하지 않은 환자 군사이 무원격전이생존율 (Distant metastasis-free survival, p=0.949) 및 전체생존율 (Overall survival, p=0.211)에서 유의한 차이는 없었다.

결론: 본 연구에서 NSM 및 동시 유방 재건술 후 NR의 발생률은 낮게 관찰 되었고 NSM 수술 결정시 종양의 생물학적 요인을 고려사항에 포함시켜야 한다.

중심 단어: 유방암, 유두 보존 유방 절제술, 유두 유륜 복합체 재발, 위험요인

Table 1. Patient, tumor, and treatment characteristics (group A)

Characteristics		Number	%
Age, years [median (range)]	43(23-67)		
	<50	774	80.5
	≥50	188	19.5
Multifocality/multicentricity	Yes	509	52.9
	No	453	47.1
No. of positive lymph nodes	0	657	68.3
	1–3	234	24.3
	≥4	71	7.4
TND, cm	≤1	364	37.8
	>1	584	60.7
	Unknown	14	1.5
Histologic type	Ductal	841	87.4
	Lobular	65	6.8
	Mixed	25	2.6
	Others	31	3.2
Histologic grade	1–2	690	71.7
	3	258	26.8
	Unknown	14	1.5
LVI	Yes	231	24.0
	No	720	74.8
	Unknown	11	1.1
ER status	Positive	703	73.1
	Negative	259	26.9
PR status	Positive	635	66.0
	Negative	327	34.0
HER2 status	Positive	275	28.6
	Negative	687	71.4
Molecular subtype	HR+/HER2-	606	63.0

	HR+/HER2+	123	12.8
	HR-/HER2+	152	15.8
	TN	81	8.4
T stage	T1	598	62.2
	T2	331	34.4
	T3	33	3.4
EIC	Positive	579	60.2
	Negative	383	39.8
Hormonal therapy	Yes	729	75.8
	No	233	24.2
Adjuvant Chemotherapy	Yes	508	52.8
	No	454	47.2
Radiation therapy	Yes	97	10.1
	No	865	89.9
Reconstruction methods	Autologous flaps	744	77.3
	Implant/TEI	218	22.7

NR, nipple-areola complex recurrence; TND, tumor-nipple distance; LVI, lymphovascular invasion; HR, hormone receptor; HER-2, human epidermal growth factor receptor 2; TN, triple negative; EIC, extensive intraductal component; NS, not significant

Table 2. Patient, tumor, and treatment characteristics (group B)

Characteristics		Number	%
Age, years [median (range)]	43 (20–65)		
	<50	159	79.9
	≥50	40	20.1
Tumor size, cm	<4	140	70.4
	≥4	59	29.6
Multifocality/multicentricity	Present	61	30.7
	Absent	138	69.4
TND, cm	≤1	74	37.2
	>1	118	59.3
	Unknown	7	3.5
Margin status	Positive, ≤1 mm	46	23.1
	>1 mm	153	76.9
Nuclear grade	1~2	166	83.4
	3	31	15.6
	Unknown	2	1.0
Comedonecrosis	Positive	126	63.3
	Negative	73	36.7
ER status	Positive	173	86.9
	Negative	21	10.6
	Unknown	5	2.5
PR status	Positive	155	77.9
	Negative	39	19.6
	Unknown	5	2.5
HER2 status	Positive	47	23.6
	Negative	147	73.9
	Unknown	5	2.5
Molecular subtype	HR+/HER2-	142	71.4
	HR+/HER2+	32	16.1

	HR-/HER2+	15	7.5
	TN	5	2.5
	Unknown	5	2.5
SLNB	Yes	182	91.5
	No	17	8.5
Hormonal therapy	Yes	15	7.5
	No	184	92.5
Reconstruction methods	Autologous flaps	130	65.3
	Implant/TEI	69	34.7

TND, tumor-to-nipple distance; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative; SLNB, sentinel lymph node biopsy; TEI, tissue expander insertion.

Table 3. Characteristics and outcomes of patients with NR

No.	Age (years)	Primary tumor			Recurrent tumor			Treatment	F/U after recurrence(m)	Status
		Stage	ER/PR/HER2	TTR(m)	Histotype	Distant metastasis	ER/PR/HER2			
1	33	1	N/N/N	42	IDC	NA	N/N/N	Excision	121	Alive
2	43	1	N/N/P	135	Paget	NA	N/N/P	Excision	27	Alive
3	33	1	N/N/N	57	DCIS	NA	P/P/N	Excision+HT	94	Alive
4	32	1	N/N/P	30	Paget	NA	NA	Excision	120	Alive
5	29	1	N/N/P	35	Paget	NA	N/N/P	Excision+RT	109	Alive
6	41	1	P/P/P	77	Paget	NA	P/N/P	Excision	65	Alive
7	26	1	P/P/N	54	IDC	NA	P/P/N	Excision+RT+HT	82	Alive
8	40	1	P/P/N	84	DCIS	Liver, bone	P/P/N	Excision+RT+HT	48	Alive
9	39	1	N/N/P	29	DCIS+Paget	NA	N/N/P	Excision	95	Alive
10	32	2	P/P/N	44	IDC	NA	P/P/N	Excision+CTx+HT	71	Alive
11	32	1	P/P/N	11	IDC	NA	N/P/N	Excision+HT	101	Alive
12	37	2	N/N/N	7	IDC	NA	N/N/N	Excision+CTx	100	Alive
13	34	2	P/P/N	58	IDC	NA	P/P/N	Excision+HT	45	Alive
14	38	1	N/N/P	43	DCIS+Paget	NA	NA	Excision	55	Alive
15	37	1	P/P/N	29	IDC	NA	P/P/N	Excision+HT	66	Alive
16	48	1	N/N/P	61	DCIS+Paget	NA	N/N/P	Excision	32	Alive

17	37	2	P/P/N	59	IDC	NA	P/P/N	Excision+RT+HT	34	Alive
18	48	1	N/N/P	23	DCIS+Paget	NA	N/N/P	Excision	70	Alive
19	44	1	P/P/N	48	IDC	NA	P/P/N	Excision+RT+HT	38	Alive
20	46	1	P/N/N	25	DCIS+Paget	NA	NA	Excision+HT	60	Alive
21	35	1	N/N/P	44	DCIS+Paget	NA	N/N/P	Excision	40	Alive
22	30	1	N/N/P	42	DCIS	NA	NA	Excision+RT	42	Alive
23	33	1	N/N/P	24	DCIS+Paget	NA	N/N/P	Excision	57	Alive
24	35	1	N/N/P	25	DCIS+Paget	NA	N/N/P	Excision	55	Alive
25	51	2	P/P/N	45	IDC	NA	P/N/N	Excision+HT	33	Alive
26	34	1	N/N/P	23	DCIS+Paget	NA	N/N/P	Excision	52	Alive
27	40	1	P/P/N	13	IDC	NA	P/P/N	Excision+RT+HT	59	Alive
28	31	1	N/N/P	14	IDC	Contralateral ALN	N/N/P	Excision+RT+CTx+Herceptin	55	Alive
29	54	2	N/N/N	28	IDC	NA	P/N/N	Excision+ALND+RT+CTx+HT	39	Alive
30	54	2	N/N/P	62	IDC	NA	N/N/P	Excision+RT	5	Alive
31	41	1	N/N/P	51	DCIS+Paget	NA	N/N/P	Excision+RT	12	Alive
32	39	1	P/P/P	54	mIDC+Paget	NA	N/N/P	Excision+HT	8	Alive
33	33	1	N/N/P	36	DCIS+Paget	NA	N/N/P	Excision+RT+CTx+Herceptin	25	Alive
34	39	1	N/N/P	18	DCIS+Paget	NA	NA	Excision	33	Alive
35	26	1	N/N/P	27	DCIS	NA	N/N/P	Excision+RT	22	Alive

36	43	1	P/P/N	8	DCIS	NA	NA	Excision+HT	40	Alive
37	46	1	P/P/P	35	DCIS+Paget	NA	P/N/P	Excision+HT	11	Alive
38	43	1	N/N/P	17	DCIS	NA	N/N/P	Excision+RT	25	Alive
39	33	1	N/N/P	15	Paget	NA	N/N/P	Excision	18	Alive
40	32	0	P/P/N	94	DCIS	NA	P/P/N	Excision	48	Alive
41	32	0	N/N/P	48	IDC	Lung, bone	N/N/P	Excision+ALND+RT+CTx+Herceptin	74	Dead
42	49	0	N/N/P	24	Paget	NA	NA	Excision	104	Alive
43	50	0	N/N/P	36	DCIS+Paget	NA	NA	Excision	87	Alive
44	48	0	N/N/P	41	DCIS+Paget	NA	N/N/P	Excision	79	Alive
45	30	0	P/N/N	23	IDC	NA	P/N/N	Excision+RT+CTx+HT	80	Alive

NR, nipple-areola complex recurrence; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; TTR, time to recurrence; F/U, follow-up; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; mIDC, microinvasive ductal carcinoma; ALN, axillary lymph node; HT, hormonal therapy; RT, radiation therapy; CTx, chemotherapy; ALND, axillary lymph node dissection; P, positive; N, negative; NA, not applicable.

Table 4. Univariate analysis of clinical and pathologic factors associated with NR (group A)

Variables		5-Year NR, n (%)	*P* value
Age, years	<50	32 (4.1)	0.073
	≥50	2 (1.1)	
Multifocality/multicentricity	Yes	27 (5.3)	0.003
	No	7 (1.6)	
No. of positive lymph nodes	0	30 (4.6)	0.088
	1–3	4 (1.7)	
	≥4	0 (0.0)	
TND	>1 cm	15 (2.6)	0.06
	≤1 cm	19 (5.2)	
	Unknown	NA	
Histologic type	Ductal	33 (3.9)	0.54
	Lobular	0 (0.0)	
	Mixed	0 (0.0)	
	Others	1 (3.2)	
Histologic grade	1–2	12 (1.7)	<0.001
	3	18 (7.0)	
	Unknown	NA	
LVI	Yes	4 (1.7)	0.20
	No	29 (4.0)	
	Unknown	NA	
Molecular subtype	HR+/HER2-	11 (1.8)	<0.001
	HR+/HER2+	2 (1.6)	
	HR-/HER2+	17 (11.2)	
	TN	4 (4.9)	
T stage	T1	28 (4.7)	0.089
	T2	6 (1.8)	
	T3	0 (0.0)	
EIC	Positive	27 (4.7)	0.008

	Negative	7 (1.8)

NR, nipple-areola complex recurrence; TND, tumor-nipple distance; LVI, lymphovascular invasion; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative; EIC, extensive intraductal component; NA, not applicable.

Table 5. Multivariate analyses of the factors associated with NR (group A)

Variables	HR	95% CI	*P*-value
Multifocality/multicentricity	3.309	1.501–7.294	0.003
Histologic grade	2.641	1.132–6.160	0.025
EIC	3.338	1.262–8.824	0.015
Molecular subtype			
HR+/HER2-	1 (reference)		
HR+/HER2+	0.972	0.261–3.620	0.966
HR-/HER2+	3.051	1.194–7.796	0.020
TN	1.511	0.376–6.066	0.561

NR, nipple-areola complex recurrence; HR, hazard ratio; CI, confidence interval; EIC, extensive intraductal component; HR (molecular subtype), hormone receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative.

Table 6. Univariate analysis of clinical and pathologic factors associated with NR (group B)

Variables		10-year NR, n (%)	P-value
Age, years	<50	5 (3.1)	0.831
	≥50	1 (2.5)	
Tumor size, cm	<4	3 (2.1)	0.268
	≥4	3 (5.1)	
Multifocality/multicentricity	Yes	0 (0.0)	0.098
	No	6 (4.4)	
TND, cm	≤1	4 (5.4)	0.150
	>1	2 (1.7)	
	Unknown	NA	
Margin status	Positive, ≤1 mm	3 (6.5)	0.113
	>1 mm	3 (2.0)	
Nuclear grade	1~2	3 (1.8)	0.019
	3	3 (9.7)	
	Unknown	NA	
Comedonecrosis	Positive	5 (4.0)	0.302
	Negative	1 (1.4)	
ER status	Positive	2 (1.2)	<0.001
	Negative	4 (19.0)	
	Unknown	NA	
PR status	Positive	1 (0.6)	<0.001
	Negative	5 (12.8)	
	Unknown	NA	
HER2 status	Positive	4 (8.5)	0.014
	Negative	2 (1.4)	
	Unknown	NA	
Molecular subtype	HR+/HER2-	2 (1.4)	<0.001
	HR+/HER2+	NA	
	HR-/HER2+	4 (26.7)	

	TN	NA
	Unknown	NA

NR, nipple-areola complex recurrence; TND, tumor-to-nipple distance; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative; NA, not applicable.

Table 7. NR after NSM in published studies

Study (year)	Study period	No. of NSMs	Inclusion criteria	F/U (months)	NR rate	Risk factors addressed for NR
Petit et al.[14] (2012)	2002-2007	934	IC, in situ disease	50	0.8% for invasive carcinoma, 2.9% for in situ disease	Tumor size, receptor status, HER2/neu status, grade, and Ki-67
Shimo et al.[13] (2016)	2000-2013	425	Breast cancer	46.8	2.3%	Young age, estrogen receptor negativity, HER2 overexpression, and HER2-enriched subtype
Sakurai et al.[12] (2013)	1985-2004	788	Breast cancer	78	3.7%	NA
Galimberti et al.[17] (2018)	2003-2011	1,989	IC, in situ disease	94	1.6% for invasive carcinoma, 3.2% for in situ disease	NA
Leclère et al.[27] (2014)	2000-2010	19	DCIS	85	5.3%	NA
Lago et al.[26] (2018)	1984-2016	69	DCIS	143	1.4%	NA
Our study (2019)	2003-2015	1,161	IC, DCIS	85 for IC, 97 for DCIS	4.1% for invasive carcinoma, 3.0% for DCIS	IC: Multifocality/multicentricity, HR-/HER2+ subtype, grade, and EIC DCIS: Receptor status, HER2+, grade, HR-/HER2+ subtype

NR, nipple-areola complex recurrence; NSM, nipple-sparing mastectomy; IC, invasive carcinoma; DCIS, ductal carcinoma in situ; F/U, follow-up; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; EIC, extensive intraductal component; NA, not available.

Figure 1. Intraoperative frozen section examination of the retroareolar margin

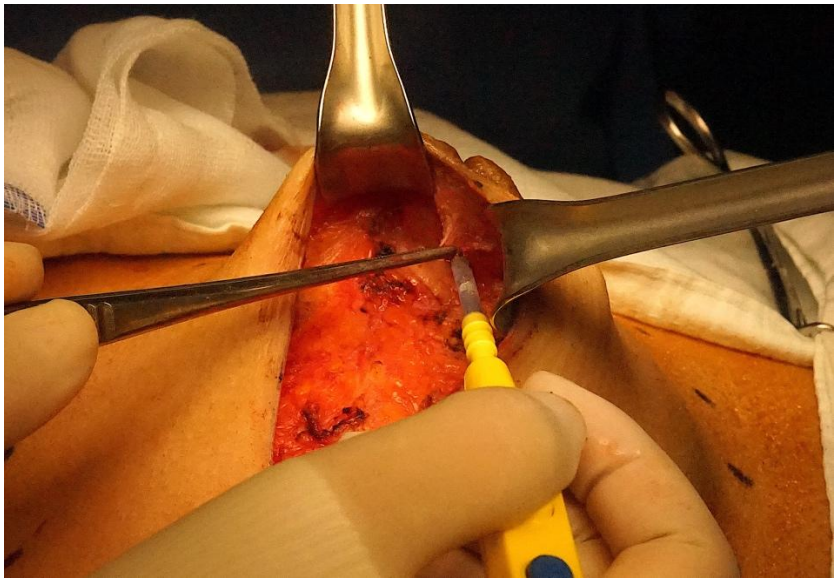

Figure 2. Distant metastasis-free survival (A) and overall survival (B) according to NR status (group A). Kaplan–Meier curves are used to estimate distant metastasis-free survival and overall survival in patients who had NR compared with patients who did not have NR. NR, nipple-areola complex recurrence.