Radiology

ORIGINAL RESEARCH • BREAST IMAGING

Resolution of Nonmass Enhancement Extension to the Nipple at Breast MRI after Neoadjuvant Chemotherapy: Pathologic Response and Feasibility for Nipple-sparing Mastectomy

*Soong June Bae, MD** • *Sung Gwe Ahn, MD, PhD** • *Eun Ji Park, MD* • *Na Lae Eun, MD* • *Jee Hung Kim, MD* • *Jung Hwan Ji, MD* • *Yoonwon Kook, MD* • *Ji Soo Jang, MD* • *Seung Ho Baek, MD* • *Yoon Jin Cha, MD, PhD* • *Joon Jeong, MD, PhD*

From the Department of Surgery (S.J.B., S.G.A., E.J.P., Y.K., J.S.J., S.H.B., J.J.), Department of Radiology (N.L.E.), Division of Medical Oncology, Department of Internal Medicine (J.H.K.), and Department of Pathology (Y.J.C.), Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul, 06273, Republic of Korea; Institute for Breast Cancer Precision Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea (S.J.B., S.G.A., J.H.K., Y.K., J.S.J., S.H.B., Y.J.C., J.J.); and Department of Surgery, Catholic Kwandong University International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Republic of Korea (J.H.J.). Received July 13, 2022; revision requested August 29; revision received November 22; accepted December 7. **Address correspondence to** J.J. (email: *gsjjoon@yuhs.ac*).

* S.J.B. and S.G.A. contributed equally to this work.

Conflicts of interest are listed at the end of this article.

See also the editorial by Lee in this issue.

Radiology 2023; 307(2):e221777 • https://doi.org/10.1148/radiol.221777 • Content codes: BR MR

Background: Nipple-sparing mastectomy (NSM) is usually contraindicated in patients with nonmass enhancement (NME) extension to the nipple at breast MRI. However, little is known about the feasibility of NSM when NME extension to the nipple resolves after neoadjuvant chemotherapy (NAC).

Purpose: To evaluate whether NSM is an appropriate surgical procedure for patients in whom NME extension to the nipple resolves after NAC.

Materials and Methods: This retrospective study included 383 women with NME at baseline MRI who underwent NAC followed by mastectomy between January 2007 and March 2022 at a single institution. NME extension to the nipple was assessed using breast MRI before NAC (hereafter, pre-NAC) and after NAC (hereafter, post-NAC). In 326 women who underwent mastectomy with removal of the nipple-areolar complex, the rate of pathologic analysis–confirmed tumor invasion of the nipple compared with NME extension to the nipple at post-NAC breast MRI was evaluated. Tumor involvement of the nipple was also assessed in those with complete pathologic response at posttreatment MRI. Furthermore, the outcomes in 57 women undergoing NSM were investigated, particularly in patients with NME extension to the nipple at initial diagnosis.

Results: Of the 326 women who underwent mastectomy with removal of the nipple-areolar complex (mean age, 49 years ± 9.4 [SD]), 217 patients (67%) showed NME extension to the nipple on pre-NAC MRI scans. Among the 153 women (70%) in whom the NME extension to the nipple resolved after NAC, the rate of pathologic analysis–confirmed tumor invasion of the nipple was 2.6% (four of 153 women; 95% CI: 0, 6.5). No pathologic analysis–confirmed tumor invasion of the nipple was detected in 31 women with complete response at MRI. Of the 57 women who underwent NSM, 12 (21%) with resolution of NME extension to the nipple after NAC had no relapse during the median follow-up of 31 months (range, 11–80 months).

Conclusion: Pathologic analysis–confirmed tumor invasion of the nipple was rare in women with resolution of nonmass enhancement extension to the nipple after neoadjuvant chemotherapy (NAC). Therefore, nipple-sparing mastectomy could be feasible in this population, especially in those with complete MRI response to NAC.

Supplemental material is available for this article.

Neoadjuvant chemotherapy (NAC) is an established treatment for stage II–III breast cancer (1). NAC allows breast cancer downstaging, which subsequently increases the rate of breast-conserving surgery. Nevertheless, about half of these patients undergo mastectomy (2). Nipple-sparing mastectomy (NSM) is a surgical procedure that removes only the underlying breast tissue and leaves the skin, areola, and nipple intact. Compared with skin-sparing or conventional mastectomy, NSM has similar oncologic and surgical safety with superior cosmetic outcomes and improved patient satisfaction (3–9). Therefore, with data supporting its oncologic safety, NSM is a feasible surgical approach in patients with breast cancer who underwent NAC (10–12).

Clinical or radiologic suspicion of nipple involvement is a contraindication for NSM, although several studies reported that patients with a short tumor-to-nipple distance without nipple involvement at preoperative imaging may be eligible for NSM (13–15). Nonmass enhancement (NME) extension to the nipple rather than the direct

Abbreviations

HER2 = human epidermal growth factor 2, NAC = neoadjuvant chemotherapy, NME = nonmass enhancement, NSM = nipple-sparing mastectomy

Summary

Pathologic analysis–confirmed tumor invasion of the nipple was rare in patients with resolution of nonmass enhancement extension to the nipple at breast MRI after neoadjuvant chemotherapy; thus, nipple-sparing mastectomy may be feasible.

Key Results

- In a retrospective study of 383 women, nonmass enhancement (NME) extension to the nipple resolved after neoadjuvant chemotherapy (NAC) in 153 of 217 women (70%) who had nipple involvement by NME at baseline breast MRI.
- The rate of pathologic analysis–confirmed tumor invasion of the nipple was only 2.6% (four of 153) in these women; it was absent in 31 women with complete MRI response to NAC.
- During the median follow-up of 31 months, no relapse occurred in the 12 women with resolution of NME to the nipple after NAC who underwent nipple-sparing mastectomy.

nipple invasion by mass-like lesion is commonly observed at preoperative breast MRI. A previous study (16) showed that the NME extension to the nipple base at preoperative MRI has a high positive predictive value for tumor invasion of the nipple that is confirmed with pathologic analysis, and it should be considered a contraindication to NSM. However, because NAC can downsize tumor extent, we assumed that patients with baseline NME extension to the nipple who responded to NAC could be eligible for NSM (17).

The purpose of our study was to evaluate whether NSM is an appropriate surgical procedure for patients in whom NME extension to the nipple resolves after NAC. We assessed pathologic nipple invasion regarding changes after NAC (hereafter, post-NAC) in NME extension to the nipple in women undergoing mastectomy with removal of the nipple-areolar complex. We further investigated outcomes of the women who presented with NME that was suspicious for cancer at baseline and were treated with NSM.

Materials and Methods

Patients

Our study protocol was reviewed and approved by the institutional review boards of the Gangnam Severance Hospital, Yonsei University (Seoul, Korea; institutional review board no. 2021-0961-001) and adhered to the tenets of the Declaration of Helsinki. The requirement for written informed consent was waived because of the retrospective study design.

Between January 2007 and March 2022, 945 women with invasive breast cancer underwent NAC followed by breast surgery at an academic medical center. From these patients, we excluded 562 women who underwent breast-conserving surgery (n = 408), did not have available pathologic information for nipple invasion (n = 4), did not have any available breast MRI before NAC (hereafter, pre-NAC) and post-NAC breast MRI (n = 9), and had only mass-like lesions not accompanying NME suspicious for cancer regardless of pre-NAC breast MRI findings of direct nipple invasion (n = 141). Finally, 383 women were included retrospectively (Fig 1). The presence of NME extension to the nipple in all women was assessed with pre- and post-NAC MRI. Of these patients, we identified 326 women undergoing mastectomy with removal of the nipple-areolar complex (Fig 1). Based on the nipple NME extension status at pre- and post-NAC MRI, women were classified into the following groups (Figs 2–5): residual NME extension to the nipple, resolution of NME extension to the nipple, new NME extension to the nipple at post-NAC MRI, and no NME extension to the nipple at pre- and post-MRI. Among these four groups, we compared the rate of pathologic analysis–confirmed tumor invasion of the nipple. Furthermore, we investigated outcomes in 57 women who underwent post-NAC NSM without NME extension to the nipple (Fig 1). Among these women, 12 had NME extension to the nipple at baseline.

Breast MRI

In 59 women, pre- and post-NAC breast MRI was performed using a 1.5-T MRI scanner (Magnetom Avanto; Siemens) with a bilateral dedicated breast coil (Matrix Breast Coil; Siemens). In 324 women, pre- and post-NAC breast MRI was performed using a 3.0-T MRI scanner (Achieva, Philips Medical System; Discovery MR750, GE Medical Systems) with a dedicated sensitivity encoding–enabled four-channel breast coil. The median intervals between the dates of pre-NAC MRI and first NAC and between the dates of post-NAC MRI and last NAC were 6 days (range, 0–30 days) and 14 days (range, 1–28 days), respectively. Bilateral axial images were acquired with women in the prone position. Dynamic contrast-enhanced 1.5-T MRI included one contrast-

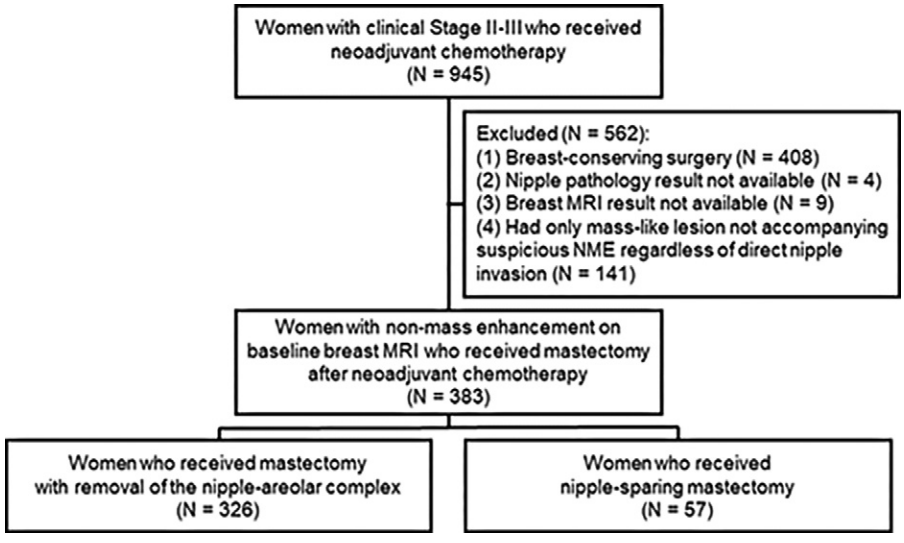

Figure 1: Study population flowchart. NME = nonmass enhancement.

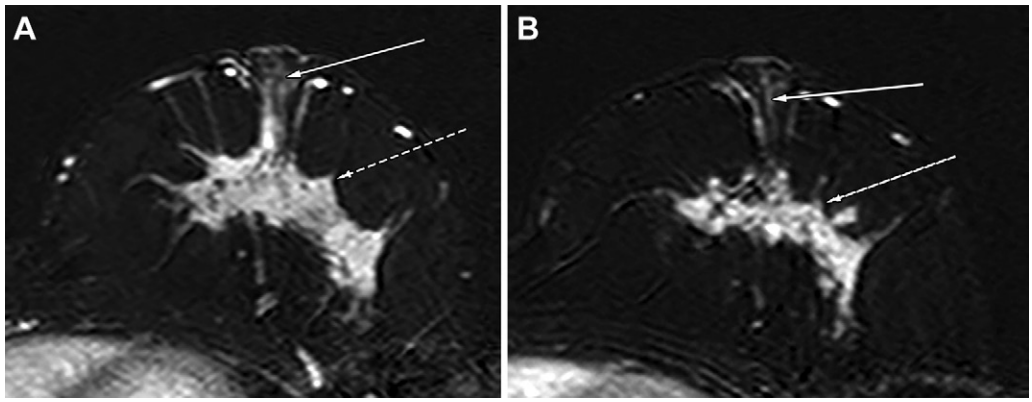

Figure 2: MRI scans in a 49-year-old woman with hormone receptor–positive and human epidermal growth factor receptor 2–negative breast cancer with nonmass enhancement (NME) extension to the nipple at MRI before and after neoadjuvant chemotherapy (NAC). The patient was administered four cycles of anthracycline and cyclophosphamide every 3 weeks, followed by 12 cycles of weekly paclitaxel. **(A)** Pre-NAC MRI scan shows a mass-like lesion (dashed arrow) with linear NME extending beyond the nipple base (solid arrow). **(B)** The mass-like lesion decreased slightly (dashed arrow), but NME extension to the nipple is still observed on the post-NAC MRI scan (solid arrow). The presence of tumor invasion of the nipple was confirmed with pathologic evaluation.

unenhanced and five contrast-enhanced series using a T1-weighted gradient-echo sequence (repetition time msec/echo time msec, 3.91/1.42; 512 × 425 matrix; flip angle, 12°; field of view, 33 × 33 cm; and section thickness, 1.5 mm). Five sequential contrast-enhanced images were acquired every minute after 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Bayer Healthcare Pharmaceuticals) or gadoterate meglumine (Dotarem; Guerbet) was injected at 2 mL/sec, followed by a 20-mL saline flush. Dynamic contrast-enhanced 3.0-T MRI included one contrast-unenhanced and five contrast-enhanced series using a T1-weighted gradient-echo sequence (4.9/2.4; 340 × 340 matrix; flip angle, 12°; field of view, 34 × 34 cm; section thickness, 1.5 mm). Contrast-enhanced images were acquired after injection of 0.1 mmol/kg of gadobutrol (Gadovist; Bayer Healthcare) with an automated injector (Nemoto; Nemoto Kyorindo) at 2 mL/sec, followed by a 20-mL saline flush. The acquisition time for each contrast-enhanced series was 74 seconds. Image subtraction was performed at all contrast-enhanced phases.

NME was evaluated using fat-suppressed T1-weighted axial images early in contrast enhancement (typically phase 1) and by using subtraction axial images. Before breast surgery, all images were prospectively reviewed by one of six radiologists with 8–20 years of experience in breast MRI. NME was considered abnormal if it was contiguous from a biopsy-proven tumor lesion with higher contrast enhancement than breast parenchymal contrast enhancement or the contralateral breast. NME extension to the nipple was defined as NME reaching or invading regions beyond the imaginary nipple base. We evaluated whether abnormal NME extended to the nipple at pre- and post-NAC breast MRI. Complete response at MRI was defined as the absence of findings suspicious for cancer in the entire breast, including the nipple and regional lymph nodes at post-NAC MRI.

Pathologic Evaluation

The nipple-areolar complex was examined for pathologic analysis–confirmed tumor invasion of the nipple in women who underwent mastectomy with removal of the nipple-areolar complex. During gross examination, the nipple-areolar complex was removed from the breast specimen and a single sagittal slice was made through the nipple. Conventional sections stained with hematoxylin-eosin were prepared from each block and reviewed. Pathologic analysis–confirmed tumor invasion of the nipple was defined as the direct infiltration of invasive carcinoma to the nipple-areolar complex or lactiferous duct involvement by intraductal carcinoma. This definition did not include dermal lymphatic emboli or Paget disease of the nipple. In women who underwent NSM, a subareolar margin was excised with a cold knife to avoid thermal injury; this margin was evaluated intraoperatively using frozen section analysis. Pathologic complete response was defined as the absence of invasive tumor cells in both the breast and axilla.

Statistical Analysis

Our primary objective was to assess whether tumor cells would persist in the nipple-areolar complex after resolution of NME extension to the nipple at post-NAC MRI. We assessed the rates of pathologic analysis–confirmed tumor invasion of the nipple in women who underwent mastectomy with removal of the nipple-areolar complex and in woment who achieved complete response at MRI after NAC in all four groups. We focused on the rate of pathologic analysis–confirmed tumor invasion of the nipple in the resolution of NME extension to the nipple group to address the main purpose of our study. To identify the clinical-pathologic factors associated with false-negative findings of a resolution of NME extension to the nipple at post-NAC MRI, we compared the characteristics of women according to the pathologic analysis–confirmed tumor invasion of the nipple within the resolution of NME extension to the nipple group. In addition, we investigated the incidence of tumor recurrence and death in the follow-up period in women who had NME extension to the nipple at baseline and who underwent subsequent NSM.

We assessed clinical-pathologic data including age at diagnosis, histologic type, histologic grade, estrogen receptor status,

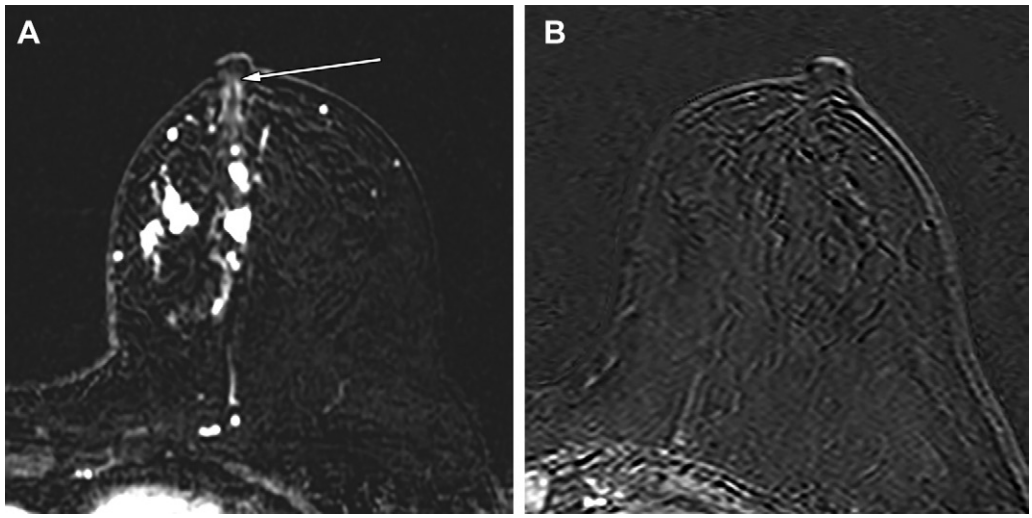

Figure 3: MRI scans in a 72-year-old woman with hormone receptor–negative and human epidermal growth factor 2–positive breast cancer with nonmass enhancement (NME) extension to the nipple at MRI before neoadjuvant chemotherapy (NAC) that appeared to have resolved at MRI after NAC. The patient was administered six cycles of docetaxel, carboplatin, trastuzumab, and pertuzumab every 3 weeks. **(A)** MRI scans acquired before NAC shows that NME invaded the nipple base (arrow). **(B)** MRI scans acquired after NAC shows complete response without residual enhancement. Pathologic complete response with the absence of tumor invasion of the nipple was confirmed at pathologic evaluation.

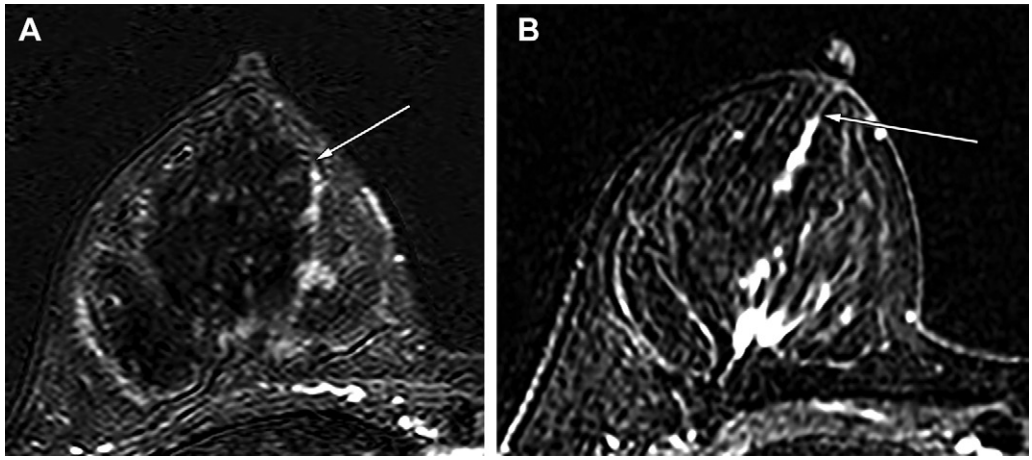

Figure 4: MRI scans in a 35-year-old woman with triple-negative breast cancer who did not have nonmass enhancement (NME) extension to the nipple at MRI before neoadjuvant chemotherapy (NAC), but who presented with NME extension at MRI after NAC. This patient was administered four cycles of anthracycline and cyclophosphamide every 3 weeks, followed by 12 cycles of weekly paclitaxel. **(A)** MRI scan before NAC shows NME not extending to the nipple (arrow). **(B)** The NME stretching the nipple-areolar complex at subareolar lesion is newly observed on the MRI scan acquired after NAC (arrow). The presence of tumor invasion of the nipple was confirmed at pathologic evaluation.

progesterone receptor status, human epidermal growth factor 2 (HER2) status, Ki-67 levels, tumor-infiltrating lymphocytes, clinical T stage, clinical N stage, pathologic T stage, pathologic N stage, and pathologic complete response. The clinical T stage and nodal status were evaluated on the basis of baseline findings at breast MRI. Clinical stages were determined according to the anatomic stage based on the American Joint Committee on Cancer guidelines (eighth edition). Pathologic data except the pathologic T stage, pathologic N stage, pathologic complete response, and tumor invasion of the nipple were obtained from core-needle biopsy samples. Continuous variables were compared by using the Student *t* test. Discrete variables were compared by using the χ^2 test or Fisher exact test. Analyses were performed using software (SPSS version 25; SPSS). *P* values less than .05 indicated statistical significance.

Results

Comparison of Baseline Characteristics

Of the 383 women included (mean age, 49 years ± 9.4 [SD]), 326 patients underwent mastectomy with removal of the nipple-areolar complex such as conventional or skin-sparing mastectomy (mean age, 49 years ± 9.4). The NAC regimens administered to these women are summarized according to breast cancer subtypes in Table S1. Among 151 women (46%) with HER2-positive breast cancer, 114 (76%) were administered six

cycles of docetaxel, carboplatin, trastuzumab, and pertuzumab (known as the TCHP regimen) for dual HER2 blockade. Forty-six of 326 women (14%) achieved complete response at MRI after NAC. Furthermore, 217 of 326 women (67%) exhibited NME extension to the nipple at pre-NAC breast MRI; among these patients, 31 women (14%) achieved complete response at MRI after NAC. The clinical T stage was higher in women with NME extension to the nipple at pre-NAC MRI than in those without enhancement to the nipple (P = .03; Table S2).

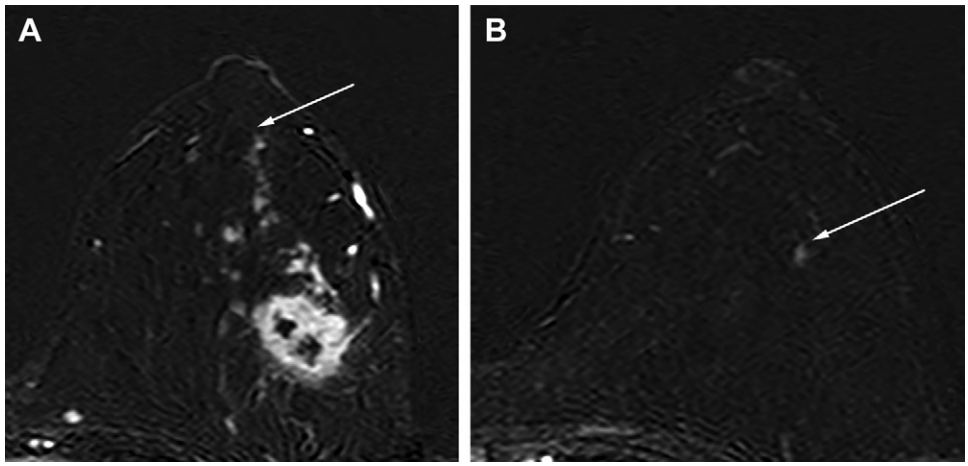

Figure 5: MRI scans in a 51-year-old woman with hormone receptor–positive and human epidermal growth factor receptor 2–negative breast cancer without nonmass enhancement (NME) extension to the nipple on MRI scans acquired before and after neoadjuvant chemotherapy (NAC). The patient was administered four cycles of anthracycline and cyclophosphamide every 3 weeks, followed by 12 cycles of weekly paclitaxel. **(A)** MRI scan acquired before NAC shows that NME extends toward the nipple but does not reach the nipple base (arrow). **(B)** After NAC, the extent of NME appears markedly reduced without NME extension to the nipple (arrow). Tumor invasion of the nipple was not found at pathologic evaluation.

Regarding pathologic analysis–confirmed tumor invasion of the nipple, 32 of 326 women (10%) exhibited tumor cells in their nipple-areolar complex. Compared with women without pathologic analysis–confirmed tumor invasion of the nipple, women with pathologic analysis–confirmed tumor invasion of the nipple were less likely to have progesterone receptor–negative or HER2-positive breast cancer and high Ki-67 levels (P = .02, .001, and .01, respectively; Table S3). In addition, the pathologic T and N stages were higher in women with pathologic analysis–confirmed tumor invasion of the nipple than in those without it (P < .001 and < .001, respectively).

Pathologic Response of Nipple-Areolar Complex according to Subgroups

The groups with residual NME extension to the nipple, resolution of NME extension to the nipple, new NME extension to the nipple at post-NAC MRI, and no NME extension to the nipple at pre- and post-NAC MRI were composed of 64 (20%), 153 (47%), two (1%), and 107 (33%) women, respectively (Fig 6). Table 1 shows a comparison of the clinical and pathologic characteristics among these groups. Hormone receptor–positive, HER2-negative breast cancer was frequently observed in the group with residual NME extension to the nipple (32 of 64; 50%). Conversely, the rate of HER2-negative breast cancer was the highest in the group with resolution of NME extension to the nipple (88 of 153; 58%; P < .001), whereas the clinical T stage was the highest in the group with residual NME extension to the nipple (P = .04; Table 1). The rate of pathologic complete response was the highest in the group with resolution of NME extension to the nipple (68 of 153; 44%), followed by the groups with no NME extension to the nipple at pre- and post-NAC MRI (28 of 107; 26%) and residual NME extension to the nipple (eight of 64; 13%). However, no woman in the group with new NME extension to the nipple at post-NAC MRI showed pathologic complete response (P < .001 for all comparisons; Table 1).

In the women with NME extension to the nipple at pre-NAC MRI, 27 patients from the group with residual NME extension to the nipple (42%; 95% CI: 30.1, 54.3) and four from the group with resolution of NME extension to the nipple (3%; 95% CI: 0, 6.5) had pathologic nipple invasion (Table 2). Among women without NME extension to the nipple at pre-NAC MRI, the NME extension to the nipple, which was suspicious for malignancy and not post-NAC contrast enhancement, was shown in two women after NAC. In these two women who showed progressive disease after NAC, one had pathologic analysis–confirmed tumor invasion of the nipple (50%; 95% CI: 37.8, 62.3). However, no patients from the group with no NME extension to the nipple at pre- and post-NAC MRI exhibited pathologic analysis–confirmed tumor invasion of the nipple (Table 2). In addition, 46 women had complete response at post-NAC MRI (31 and 15 women from the groups with resolution of NME extension to the nipple and no NME extension to the nipple at pre- and post-NAC MRI, respectively). None of these women had pathologic analysis–confirmed tumor invasion of the nipple (Table 2).

Characteristics according to Pathologic Involvement of Nipple-Areolar Complex

To identify the clinical and pathologic factors associated with the pathologic analysis–confirmed tumor invasion of the nipple in 153 women with resolution of NME extension to the nipple, we compared the characteristics according to the pathologic analysis–confirmed tumor invasion of the nipple. The pathologic T and N stages were higher in women with pathologic analysis–confirmed tumor invasion of the nipple than in those without (P = .04 and .007; respectively; Table 3). None of the four women with pathologic analysis–confirmed tumor invasion of the nipple had complete response at post-NAC MRI.

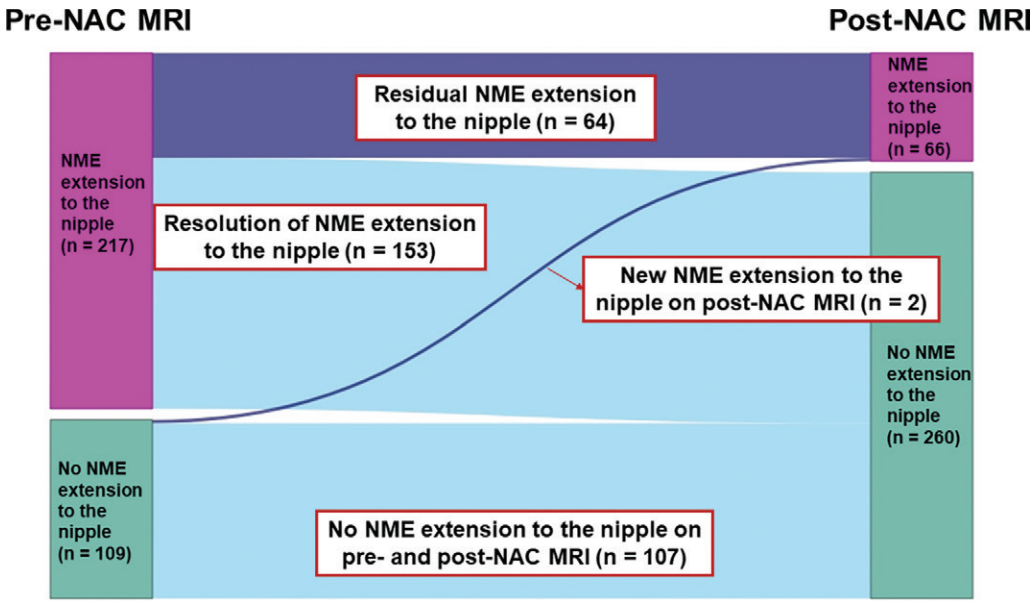

Figure 6: Diagram shows status of changes in nonmass enhancement (NME) extension to the nipple after neoadjuvant chemotherapy (NAC).

Outcomes in Women with NSM

Among the 57 women who underwent NSM after NAC (mean age, 46 years ± 8.5), 12 (21%) and 45 (79%) belonged to the group with resolution of NME extension to the nipple and the group with no NME extension to the nipple at pre- and post-NAC MRI, respectively. In all patients, intraoperative frozen section evaluation for subareolar margin indicated a tumor-free status intraoperatively, and we confirmed the same in a permanent pathologic evaluation. Respectively, seven (58%) and 11 (24%) women from the group with resolution of NME extension to the nipple and the group with no NME extension to the nipple at pre- and post-NAC MRI had complete response at MRI after NAC (P = .04). The other clinical and pathologic factors did not differ between the two groups, although the proportion of women with a progesterone receptor–negative status was higher in the group with resolution of NME extension to the nipple than in the group with no NME extension to the nipple at pre- and post-NAC MRI (P = .04; Table S4). At a median follow-up of 31 months (range, 11–80 months), no disease recurrence was observed in the group with resolution of NME extension to the nipple. However, six of 45 women (13%) in the group with no NME extension to the nipple at pre- and post-NAC MRI experienced distant invasive tumor relapse. None of these patients had complete response at MRI after NAC. See Appendix S1 for information regarding outcomes in women with residual NME extension to the nipple.

Discussion

Neoadjuvant chemotherapy (NAC) enables a reduction in the tumor burden and tumor extent in treatment of breast cancer (18,19). Therefore, its use may increase opportunities for nipple-sparing mastectomy (NSM) because it can eliminate tumor cells invading the nipple-areolar complex in patients with breast cancer extending to the nipple before NAC. Our study showed resolution of nonmass enhancement (NME) extension to the nipple after NAC (hereafter, post-NAC) in 70.5% of women who had NME extension to the nipple at initial diagnosis. Among these women (ie, the group with resolution of NME extension to the nipple), only 2.6% (none with complete response at MRI) presented with residual tumors within the nipple-areolar complex. No recurrence in the nipple, breast, or distant organs was noted in women from the group with resolution of NME extension to the nipple who underwent NSM after NAC. Our results suggest that women with post-NAC resolution of NME to the nipple, and those who achieve a complete response at MRI, could be eligible for NSM.

The resolution of NME extension to the nipple indicates that clinical response is better than the persistence of NME extension to the nipple after NAC. Pathologic complete response rate in the group with resolution of NME extension to the nipple was 45%, whereas that in the group with residual NME extension to the nipple was 12.5%. Factors associated with pathologic complete response such as high Ki-67, high tumor-infiltrating lymphocytes, and low clinical T stage were more prevalent in the group with resolution of NME extension to the nipple than in the group with residual NME extension to the nipple (20–22). In addition, 58% of the cases with resolution of NME extension to the nipple involved HER2-positive breast cancer, whereas 50% of the patients with residual NME extension to the nipple involved hormone receptor–positive, HER2-negative breast cancer. The response to NAC is poorer in patients with hormone receptor–positive, HER2-negative breast cancer than in those with HER2-positive breast cancer or triple-negative breast cancer (1,23). Moreover, 76% of the women with HER2-positive breast cancer were administered six cycles of docetaxel, carboplatin, trastuzumab, and pertuzumab, known as the TCHP regimen. The TCHP regimen increased pathologic complete response rate by more than 50% in trials (24–26). Accordingly, the better response observed in the group with resolution of NME extension to the nipple (compared with the group with residual

Table 1: Clinical and Pathologic Characteristics in Women with Mastectomy with Removal of the Nipple-Areolar Complex according to Nonmass Enhancement Change with Neoadjuvant Chemotherapy

Characteristic	Residual NME Extension to the Nipple (*n* = 64)	Resolution of NME Extension to the Nipple (*n* = 153)	New NME Extension to the Nipple at Post-NAC MRI (*n* = 2)	No NME Extension to the Nipple at Pre- and Post-NAC MRI (*n* = 107)	Total (*n* = 326)	*P* Value*
Age						.84
Mean (y)	50 ± 9.9 (26–76)	49 ± 9.6 (31–74)	37 ± 2.8 (35–39)	49 ± 8.9 (27–77)	49 ± 9.4 (26–77)	.33†
<50 y	38 (59.4)	89 (58.2)	2 (100)	62 (57.9)	191 (58.6)	
≥50 y	26 (40.6)	64 (41.8)	0	45 (42.1)	135 (41.4)	
Histologic type						.71
IDC	57 (89)	144 (94)	2 (100)	99 (92)	302 (92)	
ILC	3 (5)	5 (3)	0	4 (4)	12 (4)	
Other	4 (6)	4 (3)	0	4 (4)	12 (4)	
HG‡						.83
I or II	32 (86)	81 (82)	2 (100)	56 (80)	171 (82)	
III	5 (14)	18 (18)	0	14 (20)	37 (18)	
ER						.02
Positive	41 (64)	66 (43)	0	53 (49)	160 (49)	
Negative	23 (36)	87 (57)	2 (100)	54 (51)	166 (51)	
PR						.04
Positive	29 (45)	42 (27)	0	39 (36)	110 (34)	
Negative	35 (55)	111 (73)	2 (100)	68 (64)	216 (66)	
HER2						<.001
Positive	20 (31)	88 (58)	0	43 (40)	151 (46)	
Negative	40 (69)	65 (42)	2 (100)	64 (60)	175 (54)	
Subgroup						<.001
HR positive and HER2 negative	32 (50)	35 (23)	0	36 (34)	103 (32)	
HER2 positive	20 (31)	88 (57)	0	43 (40)	151 (46)	
TNBC	12 (19)	30 (20)	2 (100)	28 (26)	72 (22)	
Ki-67‡						.05
<14%	15 (56)	16 (30)	0	8 (26)	39 (35)	
≥14%	12 (44)	38 (70)	1 (100)	23 (74)	74 (65)	
TIL‡						.11
<20%	29 (78)	60 (60)	1 (50)	40 (57)	130 (62)	
≥20%	8 (22)	40 (40)	1 (50)	30 (43)	79 (38)	
pCR						<.001
Yes	8 (13)	68 (44)	0	28 (26)	104 (32)	
No	56 (87)	85 (56)	2 (100)	79 (74)	222 (68)	
cT stage						.04
II	13 (20)	47 (31)	1 (50)	44 (41)	105 (32)	
III	37 (58)	87 (57)	1 (50)	54 (51)	179 (55)	
IV	14 (22)	19 (12)	0	9 (8)	42 (13)	
cN stage						.84
Positive	59 (92)	141 (92)	2 (100)	101 (94)	303 (93)	
Negative	5 (8)	12 (8)	0	6 (6)	23 (7)	

Note.—Unless otherwise indicated, data are numbers of patients and data in parentheses are percentages. Mean data are ± SDs, with ranges in parentheses. cN stage = clinical N stage, cT = clinical T stage, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HG = histologic grade, HR = hormone receptor, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, NAC = neoadjuvant chemotherapy, NME = nonmass enhancement, pCR = pathologic complete response, PR = progesterone receptor, TIL = tumor-infiltrating lymphocyte, TNBC = triple-negative breast cancer.

* Unless otherwise noted, *P* values were obtained with the Fisher exact test.

† *P* value was obtained with the Student *t* test.

‡ Missing values.

Table 2: Pathologic Analysis–confirmed Tumor Invasion of the Nipple according to the Nonmass Enhancement Change with Neoadjuvant Chemotherapy

NME Change	Pathologic Analysis–confirmed Tumor Invasion of the Nipple	No Pathologic Analysis–confirmed Tumor Invasion of the Nipple	Total
Women who underwent mastectomy with removal of the nipple-areolar complex*			
Residual NME extension to the nipple	27 (42) [30.1, 54.3]	37 (58) [45.7, 69.9]	64
Resolution of NME extension to the nipple	4 (3) [0, 6.5]	149 (97) [93.5, 100]	153
New NME extension to the nipple on post-NAC MRI	1 (50) [37.8, 62.3]	1 (50) [37.8, 62.3]	2
No NME extension to the nipple on pre- and post-NAC MRI	0	107 (100)	107
Women with complete MRI response who received nipple-sacrificing surgery*			
Resolution of NME extension to the nipple	0	31 (100)	31
No NME extension to the nipple on pre- and post-NAC MRI	0	15 (100)	15

Note.—Unless otherwise indicated, data are numbers of women; data in parentheses are percentages and data in brackets are 95% CIs. NAC = neoadjuvant chemotherapy, NME = nonmass enhancement.

* Mastectomy with removal of the nipple-areolar complex includes conventional mastectomy and skin-sparing mastectomy.

NME extension to the nipple) seems reasonable. Future improvements in neoadjuvant systemic therapy may expand NSM eligibility even in patients with pathologic findings of nipple invasion at an initial diagnosis (27).

The frequency of pathologic nipple invasion in the group with resolution of NME extension to the nipple was low (2.6%); however, its presence could have increased the risk of nipple tumor recurrence. No statistically significant factors were identified at comparison of the pre-NAC clinical-pathologic characteristics between women with and without pathologic analysis–confirmed tumor invasion of the nipple in the group with resolution of NME extension to the nipple (Table 3). However, pathologic analysis–confirmed tumor invasion of the nipple was not found in women with cT2 or complete response at MRI. Therefore, in patients with cT2 or smaller tumors and in women showing complete response at MRI, NSM could be considered if NME extension to the nipple is resolved after NAC.

Pathologic analysis–confirmed tumor invasion of the nipple was observed in 42% of women with NME extension to the nipple persisting after NAC, whereas our previous findings (16) showed that a rate of pathologic analysis–confirmed tumor invasion of the nipple was 85.7% with serial sections of entire nipple-areolar complex. This discrepancy may be because of differences in the pathologic evaluation protocols: Unlike in our previous study, pathologic analysis–confirmed tumor invasion of the nipple in our present study was assessed using a single sagittal section of the nipple-areolar complex. The previous studies (28–30) that did not perform pathologic analysis with serial slices of whole nipple-areolar complex have reported rates of pathologic analysis–confirmed tumor invasion in the nipple that are 39%–62%. This is similar to our findings. In addition, preoperative chemotherapy may affect the positive predictive value of sustained NME extension to the nipple, and further research to understand clinical and radiologic characteristics of posttreatment NME is warranted. Considering our protocol for pathologic examination of the nipple-areolar complex, the pathologic invasion rate was expected to be higher in the group with residual NME extension to the nipple. Therefore, the patients with persistent NME extension to the nipple after NAC should be considered ineligible for NSM.

Our study had several limitations. First, the interobserver and intraobserver variabilities were not evaluated in this study because of its retrospective nature and the relatively long span. However, radiologists interpreting the images had more than 8 years of breast MRI experience. Second, differences in MRI techniques during the study period may have affected the reproducibility of our findings. Nevertheless, the diagnostic performance of this imaging modality may be improved through further research and continuous advancement of MRI facilities. Another limitation is that the NAC regimen changed over time. However, improvements in NAC regimens are expected to expand NSM eligibility by increasing the rates of resolution of NME extension to the nipple. Finally, although no recurrence occurred in women with resolution of NME extension to the nipple who underwent NSM, the sample size and follow-up period were insufficient to address the oncologic safety of NSM. A previous study (10) described a similar finding of no recurrence at the nipple during a mean follow-up of 73 months in patients who initially presented with tumor extension in the subareolar area. However, the analysis was conducted in a relatively small cohort. More studies with larger cohorts and sufficient follow-up periods are needed to verify our findings.

In conclusion, nonmass enhancement (NME) extension to the nipple resolved after neoadjuvant chemotherapy (NAC) in approximately 70% of the women who presented with it at breast MRI before NAC. Pathologic analysis–confirmed tumor invasion of the nipple was scarce in these women, particularly in women with complete response at MRI after NAC. Accordingly, nipple-sparing mastectomy (NSM) may be a feasible surgical

Table 3: Clinical and Pathologic Characteristics according to the Pathologic Analysis–confirmed Tumor Invasion of the Nipple in Women with Resolution of Nonmass Enhancement Extension to the Nipple after Neoadjuvant Chemotherapy

Characteristic	Pathologic Analysis–confirmed Tumor Invasion of the Nipple (*n* = 4)	No Pathologic Analysis–confirmed Tumor Invasion of the Nipple (*n* = 149)	Total (*n* = 153)	*P* Value*
Age				.64
Mean (y)	48 ± 7.5 (42–59)	49 ± 9.6 (31–74)	49 ± 9.6 (31–74)	.77†
<50 y	3 (75)	86 (58)	89 (58)	
≥50 y	1 (25)	63 (42)	64 (42)	
Histologic type				.22
IDC	3 (75)	141 (94)	144 (94)	
ILC	1 (25)	4 (3)	5 (3)	
Other	0	4 (3)	4 (3)	
HG‡				.56
I or II	3 (75)	78 (82)	81 (82)	
III	1 (25)	17 (18)	18 (18)	
ER				.63
Positive	1 (25)	65 (44)	66 (43)	
Negative	3 (75)	84 (56)	87 (57)	
PR				>.99
Positive	1 (25)	41 (28)	42 (28)	
Negative	3 (75)	108 (72)	111 (72)	
HER2				.31
Positive	1 (25)	87 (58)	88 (58)	
Negative	3 (75)	62 (42)	65 (42)	
Subgroup				.13
HR-positive and HER2-negative	1 (25)	34 (23)	35 (23)	
HER2-positive	1 (25)	87 (58)	88 (57)	
TNBC	2 (50)	28 (19)	30 (20)	
Ki-67‡				>.99
<14%	0	16 (30)	16 (30)	
≥14%	1 (100)	37 (70)	38 (70)	
TIL‡				>.99
<20%	2 (50)	58 (60)	60 (60)	
≥20%	2 (50)	38 (40)	40 (40)	
pCR				.13
Yes	0	68 (46)	68 (44)	
No	4 (100)	81 (54)	85 (56)	
Complete response at MRI				.58
Yes	0	31 (21)	31 (20)	
No	4 (100)	118 (79)	122 (80)	
cT stage				.44
II	0	47 (31)	47 (31)	
III	4 (100)	83 (56)	87 (57)	
IV	0	19 (13)	19 (12)	
cN stage				>.99
Positive	4 (100)	137 (92)	141 (92)	
Negative	0	12 (8)	12 (8)	
ypT stage				.04
0	0	61 (41)	61 (40)	
Tis	0	12 (8)	12 (8)	
I	1 (25)	41 (27)	42 (27)	
II	2 (50)	31 (21)	33 (22)	
III	1 (25)	4 (3)	5 (3)	
ypN stage				.007
0	0	96 (65)	96 (63)	
I	1 (25)	30 (20)	31 (20)	
II	2 (50)	15 (10)	17 (11)	
III	1 (25)	8 (5)	9 (6)	

Note.—Unless otherwise noted, values are the numbers of patients, with percentages in parentheses; mean data are ± SDs with ranges in parentheses. cN stage = clinical N stage, cT stage = clinical T stage, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HG = histologic grade, HR = hormone receptor, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, NME = nonmass enhancement, pCR = pathologic complete response, PR = progesterone receptor, TIL = tumor-infiltrating lymphocyte, Tis = tumor in situ, TNBC = triple-negative breast cancer, ypN stage = pathologic N stage, ypT stage = pathologic T stage.

* Unless otherwise noted, *P* values were obtained with the Fisher exact test.

† *P* value was obtained with the Student *t* test.

‡ Missing values.

procedure in women with resolution of NME extension to the nipple at breast MRI after NAC. Further research with a large cohort is warranted to establish the oncologic safety of NSM in this subpopulation.

Author contributions: Guarantors of integrity of entire study, **S.J.B., S.G.A., E.J.P., J.H.K., Y.J.C., J.J.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **S.J.B., S.G.A., J.H.K., J.H.J., Y.K.**; clinical studies, **S.J.B., S.G.A., E.J.P., N.L.E., J.H.K., J.H.J., S.H.B., Y.J.C., J.J.**; experimental studies, **J.H.K., Y.J.C.**; statistical analysis, **S.J.B., S.G.A., J.H.K., J.S.J.**; and manuscript editing, **S.J.B., S.G.A., J.H.K., Y.J.C., J.J.**

Disclosures of conflicts of interest: S.J.B. No relevant relationships. **S.G.A.** No relevant relationships. **E.J.P.** No relevant relationships. **N.L.E.** No relevant relationships. **J.H.K.** No relevant relationships. **J.H.J.** No relevant relationships. **Y.K.** No relevant relationships. **J.S.J.** No relevant relationships. **S.H.B.** No relevant relationships. **Y.J.C.** No relevant relationships. **J.J.** Chairman of the Korean Breast Cancer Society.

References

1. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384(9938):164–172.
2. Killelea BK, Yang VQ, Mougalian S, et al. Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: results from the National Cancer Database. J Am Coll Surg 2015;220(6):1063–1069.
3. Wong SM, Chun YS, Sagara Y, Golshan M, Erdmann-Sager J. National Patterns of Breast Reconstruction and Nipple-Sparing Mastectomy for Breast Cancer, 2005-2015. Ann Surg Oncol 2019;26(10):3194–3203.
4. De La Cruz L, Moody AM, Tappy EE, Blankenship SA, Hecht EM. 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):3241–3249.
5. Mota BS, Riera R, Ricci MD, et al. Nipple- and areola-sparing mastectomy for the treatment of breast cancer. Cochrane Libr 2016;11(11):CD008932.
6. 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.
7. Wu ZY, Kim HJ, Lee JW, et al. Breast Cancer Recurrence in the Nipple-Areola Complex After Nipple-Sparing Mastectomy With Immediate Breast Reconstruction for Invasive Breast Cancer. JAMA Surg 2019;154(11):1030–1037.
8. Li M, Chen K, Liu F, Su F, Li S, Zhu L. Nipple sparing mastectomy in breast cancer patients and long-term survival outcomes: An analysis of the SEER database. PLoS One 2017;12(8):e0183448.
9. 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.
10. Wu ZY, Han HH, Kim HJ, et al. A Propensity Score-matched Analysis of Long-term Oncologic Outcomes After Nipple-sparing Versus Conventional Mastectomy for Locally Advanced Breast Cancer. Ann Surg 2022;276(2):386–390.
11. Ryu JM, Park S, Paik HJ, et al. Oncologic Safety of Immediate Breast Reconstruction in Breast Cancer Patients Who Underwent Neoadjuvant Chemotherapy: Short-Term Outcomes of a Matched Case-Control Study. Clin Breast Cancer 2017;17(3):204–210.
12. Peled AW, Wang F, Foster RD, et al. Expanding the Indications for Total Skin-Sparing Mastectomy: Is It Safe for Patients with Locally Advanced Disease? Ann Surg Oncol 2016;23(1):87–91.
13. Weber WP, Haug M, Kurzeder C, et al. Oncoplastic Breast Consortium consensus conference on nipple-sparing mastectomy. Breast Cancer Res Treat 2018;172(3):523–537.
14. Wu ZY, Kim HJ, Lee J, et al. Oncologic Safety of Nipple-Sparing Mastectomy in Patients with Breast Cancer and Tumor-to-Nipple Distance ≤ 1 cm: A Matched Cohort Study. Ann Surg Oncol 2021;28(8):4284–4291.
15. Ryu JM, Nam SJ, Kim SW, et al. Feasibility of Nipple-Sparing Mastectomy with Immediate Breast Reconstruction in Breast Cancer Patients with Tumor-Nipple Distance Less Than 2.0 cm. World J Surg 2016;40(8):2028–2035.
16. Bae SJ, Cha YJ, Eun NL, et al. Diagnostic Accuracy of Nonmass Enhancement at Breast MRI in Predicting Tumor Involvement of the Nipple: A Prospective Study in a Single Institution. Radiology 2021;301(1):47–56.
17. Jadeja P, Ha R, Rohde C, et al. Expanding the Criteria for Nipple-Sparing Mastectomy in Patients With Poor Prognostic Features. Clin Breast Cancer 2018;18(3):229–233.
18. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26(5):778–785.
19. Boughey JC, Peintinger F, Meric-Bernstam F, et al. Impact of preoperative versus postoperative chemotherapy on the extent and number of surgical procedures in patients treated in randomized clinical trials for breast cancer. Ann Surg 2006;244(3):464–470.
20. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol 2018;19(1):40–50.
21. Kim SY, Cho N, Choi Y, et al. Factors Affecting Pathologic Complete Response Following Neoadjuvant Chemotherapy in Breast Cancer: Development and Validation of a Predictive Nomogram. Radiology 2021;299(2):290–300.
22. Tao M, Chen S, Zhang X, Zhou Q. Ki-67 labeling index is a predictive marker for a pathological complete response to neoadjuvant chemotherapy in breast cancer: A meta-analysis. Medicine (Baltimore) 2017;96(51):e9384.
23. Yau C, Osdoit M, van der Noordaa M, et al; I-SPY 2 Trial Consortium. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol 2022;23(1):149–160.
24. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24(9):2278–2284.
25. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;19(1):115–126.
26. Burstein HJ, Curigliano G, Thürlimann B, et al; Panelists of the St Gallen Consensus Conference. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol 2021;32(10):1216–1235.
27. Schmid P, Cortes J, Pusztai L, et al; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020;382(9):810–821.
28. Jun S, Bae SJ, Cha YJ, et al. Significance of Non-Mass Enhancement in the Subareolar Region on Preoperative Breast Magnetic Resonance Imaging for Nipple-Sparing Mastectomy. Clin Breast Cancer 2020;20(4):e458–e468.
29. Koh J, Park AY, Ko KH, Jung HK. MRI diagnostic features for predicting nipple-areolar-complex involvement in breast cancer. Eur J Radiol 2020;122:108754.
30. Sakamoto N, Tozaki M, Hoshi K, Fukuma E. Is MRI useful for the prediction of nipple involvement? Breast Cancer 2013;20(4):316–322.