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Significance of Non-Mass Enhancement  
in the Subareolar Region on  
Preoperative Breast Magnetic  
Resonance Imaging for  
Nipple-Sparing Mastectomy

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# Significance of Non-Mass Enhancement in the Subareolar Region on Preoperative Breast Magnetic Resonance Imaging for Nipple-Sparing Mastectomy

Directed by Professor Joon Jeong

The Master's Thesis  
submitted to the Department of Medicine,  
the Graduate School of Yonsei University  
in partial fulfillment of the requirements for the degree  
of Master of Medical Science

Shiyeol Jun

June 2020

This certifies that the Doctoral  
Dissertation of Shiyeol Jun is approved.

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The Graduate School  
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June 2020

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I believe medicine still has a lot to develop, and I will do my best for its development in my life as a doctor. Thank you.

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ABSTRACT

**Significance of Non-Mass Enhancement in the Subareolar Region on  
Preoperative Breast Magnetic Resonance Imaging for  
Nipple-Sparing Mastectomy**

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The eligibility for NSM regarding to subareolar NME on breast MRI was not clear. The rate of pathologic nipple invasion was as low as 6.1% when NME did not extend to the nipple on breast MRI. NSM is possible if NME does not involve the nipple on breast MRI.

**Purpose:** The eligibility for nipple-sparing mastectomy (NSM) regarding subareolar non-mass enhancement (NME) on breast magnetic resonance imaging (MRI) was not clear. This study aimed to evaluate the eligibility for NSM according to the NME-to-nipple distance on preoperative breast MRI.

**Methods:** We identified patients with breast cancer who underwent mastectomy with NME suspected of malignancy in the subareolar region on preoperative breast MRI. The incidence of nipple invasion was pathologically evaluated according to the NME-to-nipple distance on breast MRI, and the clinicopathologic factors related to pathologic nipple invasion were analyzed.

**Results:** Of 137 patients, 55 (40.1%) had NME extension to the nipple, 53 (38.7%) had radiologic distance less than 2 cm, and 29 (21.2%) had radiologic distance of 2 cm or more. The rate of pathologic nipple invasion was 52.7% (29 of 55) in patients with NME extension to nipple, 7.5% (4 of 53) in patients with NME-to-nipple distance less than 2 cm, and 3.4% (1 of 29) in patients with NME-to-nipple distance of 2 cm or more ( $P < .001$ ). NME extension to the nipple was an independent risk factor for pathologic nipple invasion (odds ratio 21.702; 95% confidence interval, 2.613-180.225;  $P = .004$ ). The survival outcome was not different between NSM and conventional total mastectomy/skin-sparing mastectomy in patients with radiologic distance less than 2 cm, but without NME extension to the nipple.

**Conclusions:** NSM is an acceptable procedure in patients with breast cancer with a low incidence of pathologic nipple invasion when there is no evidence of NME extension to the nipple on preoperative breast MRI.

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Key words : breast neoplasms, magnetic resonance imaging, mastectomy, nipple, radiographic image enhancement

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## **I. INTRODUCTION**

Breast magnetic resonance imaging (MRI) has been frequently used for the preoperative evaluation of breast cancer because it is more accurate in identifying the extent of tumor, multiple cancers, and contralateral breast cancer than conventional radiologic modalities such as ultrasound and mammography<sup>1-3</sup>. In breast MRI, the suspicious findings of cancer are classified into two categories: mass-like enhancement and non-mass enhancement (NME)<sup>4</sup>. NME causes a high proportion of false-positive diagnoses of breast cancer, and compared with mass-like enhancement, NME decreases the accuracy of breast MRI<sup>5,6</sup>.

Nipple-sparing mastectomy (NSM), a modified mastectomy to preserve the nipple-areolar complex and skin, has become an increasingly common procedure because of its excellent cosmetic outcomes<sup>7-9</sup>. Consequently, women who undergo NSM are more satisfied than those

who undergo conventional total mastectomy (TM) and skin-sparing mastectomy (SSM). In addition, numerous studies have confirmed the oncologic safety of NSM in properly selected patients with low locoregional or distant recurrence and death<sup>10-13</sup>. Therefore, the eligibility for NSM is being expanded to date. Conventionally, a distance greater than 2 cm between the tumor and nipple on radiologic evaluation is considered an indication for NSM<sup>14</sup>. Although the cut-off point of the nipple-to-tumor distance for NSM remains unclear, a recent study suggested that NSM could be performed even if the radiologic distance was less than 2 cm<sup>15-17</sup>. However, little is known whether the NME, not a mass like lesion, in the subareolar region on breast MRI should be considered a cancer and whether NSM is possible when NME extends to the nipple or how far away NME is from the nipple.

This retrospective study aimed to analyze the eligibility for NSM based on the NME-to-nipple distance on preoperative MRI. We assessed the incidence of nipple invasion based on final pathologic evaluation according to NME-to-nipple distance and clinicopathologic factors related to pathologic nipple invasion. Survival outcomes after surgical procedures (NSM vs. conventional TM and SSM) were also investigated in patients with short NME-to-nipple distance on breast MRI.

## **II. MATERIALS AND METHODS**

### **1. Patients**

From January 2013 to February 2016, 455 breast cancer patients

underwent preoperative breast MRI followed by mastectomy, including conventional TM, SSM, and NSM, at Gangnam Severance Hospital. Among these patients, we included those with NME suspected of malignancy in the subareolar region on breast MRI. In addition, we excluded patients who (i) received neoadjuvant chemotherapy, (ii) underwent breast MRI with diagnosed malignancy after breast mass excision, and, (iii) had a NME that appears to be benign lesion, and (iv) had a NME suspected of malignancy, but which was not present in the subareolar region. Finally, 137 patients were included.

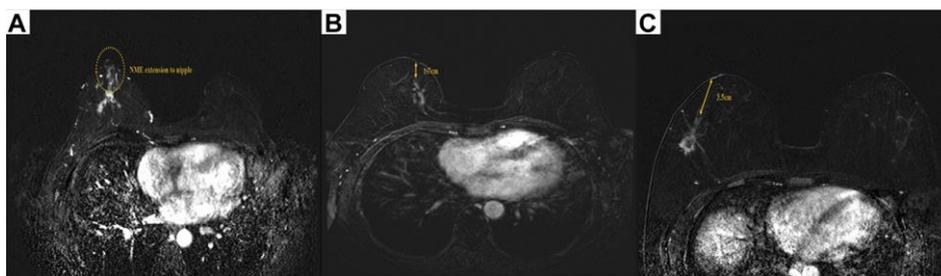
The study protocol was reviewed and approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University, Seoul, Korea and adhered to the tenets of the Declaration of Helsinki. Obtaining written informed consents was waived because of the retrospective study design.

## **2. Breast MRI**

In this study, preoperative breast MRI was performed for all patients using a 3.0-T MR imager (Achieva; Philips Medical System, Best, Netherlands) with a dedicated, sensitivity encoding (SENSE) enabled, four-channel breast coil. All patients were examined in the prone position, and bilateral axial images were obtained for all examinations. The routine protocol included turbo spin-echo T1- and T2-weighted sequences and T2-weighted fat-suppressed spin echo series. Dynamic contrast-enhanced MR images included one pre-contrast and five post-contrast series using a fat-

suppressed T1-weighted gradient echo sequence (TR/TE: 4.9/2.4; matrix, 340×340; flip angle, 12°; field of view, 34×34 cm; slice thickness, 1.5 mm). Gadobutrol (Gadovist, Bayer Healthcare, Berlin, Germany) with a dose of 0.1 mmol/kg was injected using an automated injector (Nemoto; Nemoto Kyorindo, Tokyo, Japan) at a rate of 2 mL/s, followed by a 20-mL saline flush<sup>6</sup>.

On each of fat-suppressed T1-weighted axial images corresponding to the subareolar region, the distance from the nipple to the nearest NME was measured. The radiologic distance was defined as the shortest length among the estimated distance values from nipple to NME on breast MRI. We divided the patients into three groups according to the radiologic distance: i) NME extension to the nipple (NME-to-nipple distance of 0 cm), ii) NME-to-nipple distance less than 2 cm, and iii) NME-to-nipple distance of 2 cm or more (Figure. 1).



**Figure. 1. Examples of breast MRI**

Breast MR image of (A) patients with NME extension to the nipple, (B) patients with the distance from the nipple to nearest NME was less than 2 cm, and (C) patients with the distance from the nipple to nearest NME was 2 cm or more.

### 3. Pathologic evaluation

In microscopic evaluation, the tumor size, including the diameter of the invasive portion and *in situ* portion, was measured at the level of the largest diameter. The sagittal section of the nipple-areolar complex was routinely examined in patients who underwent conventional TM or SSM at our institution. Specialized pathologists assessed whether Paget's disease, lactiferous duct involvement, or dermal lymphatic invasion by tumor cells in the nipple-areolar complex was observed; if any of the three were present, it was defined as pathologic nipple invasion. In all patients who underwent NSM, the sub-areolar margin was excised using a cold knife to avoid thermal injury, and intraoperative frozen section analysis was intraoperatively performed. Pathologic nipple invasion was defined as the presence of tumor cells in the sub-areolar margin based on intraoperative frozen or final pathologic evaluations.

### 4. Statistical analysis

Data such as age, tumor size, histologic grade (HG), lymphovascular invasion, surgical method, immediate reconstruction, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor 2 (HER2) status, Ki-67 levels, pathologic T stage, and pathologic N stage were retrospectively reviewed. TNM stage was determined according to the Guidelines of the American Joint Committee on Cancer, 7<sup>th</sup> edition. Continuous variables were compared using the Student's *t*-test. Discrete variables were compared using the chi-square test

or Fisher's exact test. Multivariable analysis of clinicopathologic factors for pathologic nipple invasion was performed using a binary logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) with two-sided *p* values were provided. The Kaplan-Meier method was used to estimate recurrence-free survival (RFS) and overall survival (OS), and the estimated survival curves were compared using the log-rank test. RFS was measured from the date of mastectomy to the date of first breast tumor recurrence, including local, regional, and systemic recurrence. OS was calculated as the duration from mastectomy to death or the last date of study follow-up (April 30, 2019). All analyses were performed using the SPSS version 23 software (SPSS; Chicago, IL, USA), and statistical significance was defined by a *p* value of <0.05.

### **III. RESULTS**

#### **1. Patient characteristics**

The baseline characteristics are summarized in Table 1. The median patient age was 50 (range, 22-78) years, and the mean radiologic distance was 1.03 (standard deviation,  $\pm 1.15$ ) cm. According to the radiologic distance between the nipple and NME, 55 (40.1%) patients had NME extension to the nipple, 53 (38.7%) patients had radiologic distance less than 2 cm, and 29 (21.2%) patients had radiologic distance 2 cm or more. The size of the ductal carcinoma in situ portion was associated with the NME-to-nipple distance, but not the size of the invasive carcinoma portion. The patients had more ER and PR negative, as the closer NME to

the nipple. In addition, there was no statistical significance, although the trend of HER2 positivity and high Ki-67 was observed.

Of all the patients, 30 (21.9%) underwent NSM. No patients with NME extension to the nipple on breast MRI underwent NSM. Among these patients, 19 (63.3%) with radiologic distance less than 2 cm and 11 (36.7%) with radiologic distance 2 cm or more underwent NSM. The patients who underwent NSM were younger (44 vs 52,  $p < 0.001$ ) and had biologic features related to good prognostic factors, such as ER positivity, PR positivity, HER2 negativity, and low Ki-67 (Table A.1). In one patient, although no tumor cells were noted in the sub-areolar margin, as determined by intraoperative frozen evaluation, the result was changed to the presence of tumor cells in the final pathologic results. Subsequently, the nipple-areolar complex was sacrificed in this patient.

**Table 1. Baseline Characteristics of the Patients According to NME-to-Nipple Distance on Breast MRI**

| Variables           | Radiologic Distance on Breast MRI |                         |                         | Total<br>(N =<br>137) | P     |
|---------------------|-----------------------------------|-------------------------|-------------------------|-----------------------|-------|
|                     | NME Extension to Nipple (n = 55)  | Distance <2 cm (n = 53) | Distance ≥2 cm (n = 29) |                       |       |
| Age, median (range) | 51 (22-78)                        | 49 (35-76)              | 49 (24-68)              | 50 (22-78)            | .279  |
| NME-to-nipple       | 0                                 | 1.08 ± 0.36             | 2.87 ± 0.78             | 1.03 ±                | <.001 |

|   |             |             |             |             |       |
|---|-------------|-------------|-------------|-------------|-------|
| <b>distance, cm, ± SD</b>                         |             |             |             | 1.15        |       |
| <b>NME size, cm, ± SD</b>                         | 4.58 ± 2.09 | 4.10 ± 1.93 | 3.37 ± 1.58 | 4.14 ± 1.97 | .026  |
| <b>DCIS size, cm, ± SD</b>                        | 4.06 ± 1.85 | 3.84 ± 2.47 | 2.86 ± 1.25 | 3.72 ± 2.06 | .032  |
| <b>Invasive cancer size, cm, ± SD<sup>a</sup></b> | 2.05 ± 1.64 | 2.21 ± 1.95 | 1.98 ± 1.28 | 2.09 ± 1.68 | .85   |
| <b>HG,<sup>a</sup> n (%)</b>                      |             |             |             |             | .098  |
| <b>1 or 2</b>                                     | 24 (55.8)   | 29 (76.3)   | 18 (75.0)   | 71 (67.6)   |       |
| <b>3</b>  | 19 (44.2)   | 9 (23.7)    | 6 (25.0)    | 34 (32.4)   |       |
| <b>LVI, n (%)</b>                                 |             |             |             |             | .922  |
| <b>Positive</b>                                   | 13 (23.6)   | 11 (20.8)   | 6 (20.7)    | 30 (21.9)   |       |
| <b>Negative</b>                                   | 42 (76.4)   | 42 (79.2)   | 23 (79.3)   | 107 (78.1)  |       |
| <b>TM method, n (%)</b>                           |             |             |             |             | <.001 |
| <b>Conventional</b>                               | 33 (60.0)   | 22 (41.5)   | 14 (48.3)   | 69 (50.4)   |       |
| <b>NSM</b>  | 0           | 19 (35.8)   | 11 (37.9)   | 30 (21.9)   |       |
| <b>SSM</b>  | 22 (40.0)   | 12 (22.6)   | 4 (13.8)    | 38 (27.7)   |       |
| <b>IR (Reconstruction),</b>                       |             |             |             |             | .067  |

|                       |           |           |           |                   |
|-----------------------|-----------|-----------|-----------|-------------------|
| <b>n (%)</b>          |           |           |           |                   |
| <b>Yes</b>            | 23 (41.8) | 34 (64.2) | 15 (51.7) | 72<br>(52.6)      |
| <b>No</b>             | 32 (58.2) | 19 (35.8) | 14 (48.3) | 65<br>(47.4)      |
| <b>T stage, n (%)</b> |           |           |           | .932 <sup>b</sup> |
| <b>0</b>              | 10 (18.2) | 12 (22.6) | 4 (13.8)  | 26<br>(19.0)      |
| <b>1</b>              | 28 (50.9) | 20 (41.5) | 15 (51.7) | 65<br>(47.4)      |
| <b>2</b>              | 15 (2.3)  | 17 (32.1) | 9 (31.0)  | 41<br>(29.9)      |
| <b>3</b>              | 2 (3.6)   | 2 (4.0)   | 1 (3.4)   | 5 (3.6)           |
| <b>N stage, n (%)</b> |           |           |           | .254              |
| <b>0</b>              | 40 (72.7) | 40 (75.5) | 17 (58.6) | 97<br>(70.8)      |
| <b>≥1</b>             | 15 (27.3) | 13 (24.5) | 12 (41.4) | 40<br>(29.2)      |
| <b>Stage, n (%)</b>   |           |           |           | .044              |
| <b>0</b>              | 10 (18.2) | 12 (22.6) | 4 (13.8)  | 26<br>(19.0)      |
| <b>1</b>              | 26 (47.3) | 19 (35.8) | 8 (27.6)  | 53<br>(38.7)      |
| <b>2</b>              | 8 (14.5)  | 18 (34.0) | 13 (44.8) | 39<br>(28.5)      |

|                        |           |           |           |                   |
|------------------------|-----------|-----------|-----------|-------------------|
| <b>3</b>               | 11 (20.0) | 4 (8.0)   | 4 (13.8)  | 19<br>(13.9)      |
| <b>ER, n (%)</b>       |           |           |           | .019              |
| <b>Positive</b>        | 33 (60.0) | 43 (81.1) | 24 (82.8) | 100<br>(73.0)     |
| <b>Negative</b>        | 22 (40.0) | 10 (18.9) | 5 (17.2)  | 37<br>(27.0)      |
| <b>PR, n (%)</b>       |           |           |           | .029              |
| <b>Positive</b>        | 25 (45.5) | 36 (67.9) | 20 (69.0) | 81<br>(59.1)      |
| <b>Negative</b>        | 30 (54.5) | 17 (32.1) | 9 (31.0)  | 56<br>(40.9)      |
| <b>HER2, n (%)</b>     |           |           |           | .078              |
| <b>Positive</b>        | 26 (47.3) | 17 (32.1) | 7 (24.1)  | 50<br>(36.5)      |
| <b>Negative</b>        | 29 (52.7) | 36 (67.9) | 22 (75.9) | 87<br>(63.5)      |
| <b>Subgroup, n (%)</b> |           |           |           | .158 <sup>b</sup> |
| <b>HR+HER2-</b>        | 25 (45.5) | 34 (64.2) | 20 (69.0) | 79<br>(57.7)      |
| <b>HR+HER2+</b>        | 8 (14.5)  | 9 (17.0)  | 4 (13.8)  | 21<br>(15.3)      |
| <b>HR-HER2+</b>        | 18 (32.7) | 8 (15.1)  | 3 (10.3)  | 29<br>(21.2)      |
| <b>TNBC</b>            | 4 (7.3)   | 2 (3.8)   | 2 (6.9)   | 8 (5.8)           |

|               |           |           |           |              |      |
|---------------|-----------|-----------|-----------|--------------|------|
| <b>Ki-67</b>  |           |           |           |              | .056 |
| <b>&lt;14</b> | 23 (41.8) | 29 (54.7) | 20 (69.0) | 72<br>(52.6) |      |
| <b>≥14</b>    | 32 (58.2) | 24 (45.3) | 9 (31.0)  | 65<br>(47.4) |      |

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HG = histologic grade; IR = immediate reconstruction; LVI = lymphovascular invasion; MRI = magnetic resonance image; NME = non-mass enhancement; NSM = nipple-sparing mastectomy; PR = progesterone receptor; SD = standard deviation; SSM = skin-sparing mastectomy; TM = total mastectomy; receptor; TNBC = triple negative breast cancer.

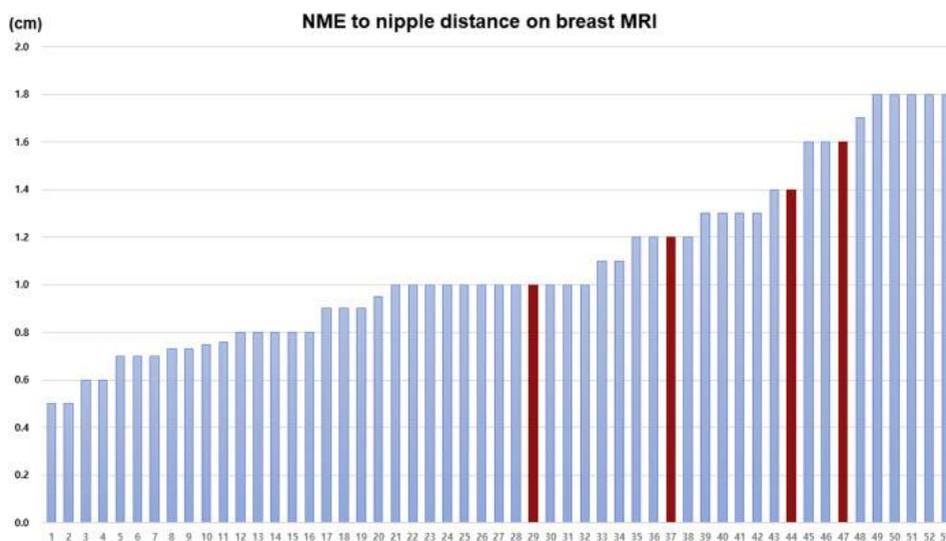
<sup>a</sup> : Missing values.

<sup>b</sup> : Fisher exact test.

## **2. Pathologic nipple invasion according to the NME-to-nipple distance**

Among the three groups according to radiologic distance, pathologic nipple invasion was observed in 29 (52.7%) of 55 patients with NME extension to the nipple, 4 (7.5%) of 53 patients with radiologic distance less than 2 cm (Figure. 2), and 1 (3.4%) of 29 patients with radiologic distance of 2 cm or more ( $p < 0.001$ , Table 2). In post-hoc analysis, there was no difference in pathologic nipple invasion between patients with NME-to-nipple distance less than 2 cm and those with NME-to-nipple distance 2 cm or more ( $p = 0.458$ ). Short radiologic distance, high-grade HG, PR negativity, and HER2 positivity were associated with

pathologic nipple invasion (Table A.2). In a multivariate analysis adjusted for other clinicopathologic parameters, NME extension to the nipple was a significant independent risk factor (OR 21.702; 95% CI, 2.613 to 180.225;  $p=0.003$ ) for pathologic nipple invasion (Table 3).



**Figure. 2. Radiologic distance in patients with NME-to-nipple distance less than 2 cm and those without NME extension to the nipple on breast MRI**

In the graph, the red bar represents the patients with nipple invasion on pathologic evaluation.

**Table 2. Nipple Invasion of Tumor on Pathologic Evaluation According to Radiologic Distance on Breast MRI**

|                     | Radiologic Distance on Breast MRI |                         |                         | <i>P</i> |
|---------------------|-----------------------------------|-------------------------|-------------------------|----------|
|                     | NME Extension to Nipple (n = 55)  | Distance <2 cm (n = 53) | Distance ≥2 cm (n = 29) |          |
| Pathology, n (%)    |                                   |                         |                         | <.001    |
| Nipple invasion (+) | 29 (52.7)                         | 4 (7.5)                 | 1 (3.4)                 |          |
| Nipple invasion (-) | 26 (47.3)                         | 49 (92.5)               | 28 (96.6)               |          |

**Table 3. Univariable and Multivariable Analysis of Factors Associated With Nipple Invasion of Tumor on Pathologic Evaluation**

| Variables                                     | Univariate             |          | Multivariate           |          |
|---|------------------------|----------|------------------------|----------|
|   | OR (95% CI)            | <i>P</i> | OR (95% CI)            | <i>P</i> |
| <b>Distance from nipple to NME on MRI, cm</b> |                        |          |                        |          |
| ≥2  | Ref                    |          | Ref                    |          |
| <2  | 2.696 (0.288-25.274)   | .385     | 2.006 (0.193-20.809)   | .560     |
| 0   | 34.577 (4.405-271.421) | .001     | 21.702 (2.613-180.225) | .004     |

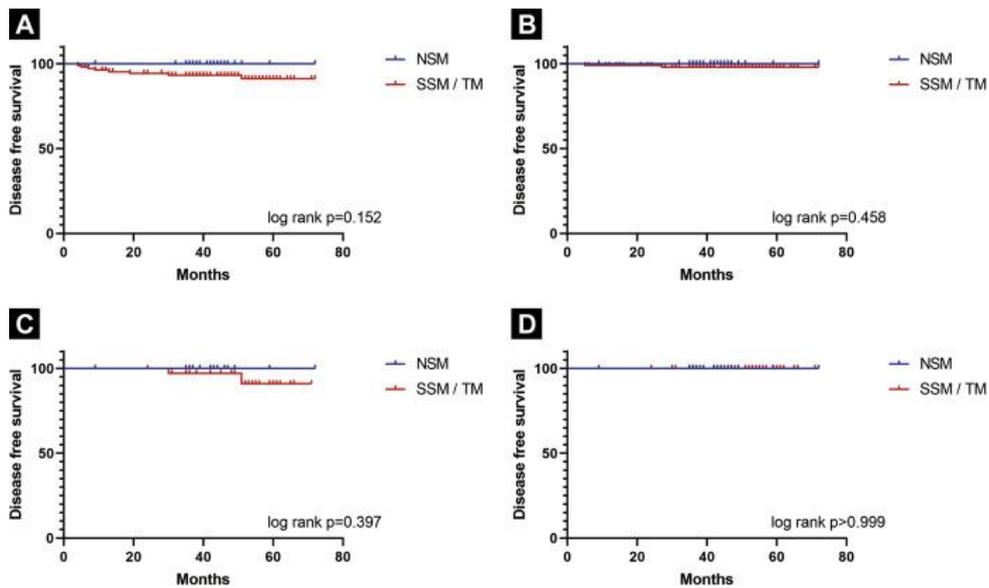
| <b>HG</b>       |        |         |      |        |         |      |
|-----------------|--------|---------|------|--------|---------|------|
| <b>1 or 2</b>   | Ref    |         | Ref  |        |         |      |
| <b>3</b>        | 3.442  | (1.368- | .009 | 2.450  | (0.780- | .125 |
|                 | 8.661) |         |      | 7.693) |         |      |
| <b>ER</b>       |        |         |      |        |         |      |
| <b>Positive</b> | Ref    |         | -    |        |         |      |
| <b>Negative</b> | 2.038  | (0.889- | .092 | -      | -       |      |
|                 | 4.668) |         |      |        |         |      |
| <b>PR</b>       |        |         |      |        |         |      |
| <b>Positive</b> | Ref    |         | Ref  |        |         |      |
| <b>Negative</b> | 3.138  | (1.406- | .005 | 1.355  | (0.385- | .636 |
|                 | 7.005) |         |      | 4.772) |         |      |
| <b>HER2</b>     |        |         |      |        |         |      |
| <b>Positive</b> | Ref    |         | Ref  |        |         |      |
| <b>Negative</b> | 2.496  | (1.130- | .024 | 0.874  | (0.252- | .814 |
|                 | 5.512) |         |      | 3.027) |         |      |

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HG = histologic grade; LVI = lymphovascular invasion; MRI = magnetic resonance image; NME = non-mass enhancement; PR = progesterone receptor.

### 3. Survival outcomes according to surgical method

During the median follow-up of 47 (range, 5-72) months, we analyzed RFS and OS according to NSM. When analyzing the survival outcome, one patient who underwent NSM followed by excision of the

nipple-areolar complex owing to changes in the pathological results was considered to have undergone SSM. Among the total patients, 8 patients had breast tumor recurrence and 2 died. No recurrence or death were noted in the 29 patients who underwent NSM. There was no significant difference in RFS and OS between the patients underwent NSM and the patients underwent SSM or TM ( $p=0.152$  and  $p=0.458$ , respectively; Figure. 3A, B). When survival outcomes were analyzed in 53 patients with a radiologic distance less than 2 cm, there was no difference in RFS and OS according to NSM ( $p=0.397$  and  $p>0.999$ , respectively; Figure. 3C, D).



**Figure. 3. Recurrence-free survival and overall survival according to nipple-sparing mastectomy.** (A) Recurrence-free survival and (B) overall survival in all patients ( $n=137$ ), and (C) recurrence-free survival and (D) overall survival in patients with the distance from the nipple to nearest NME was less than 2 cm ( $n=53$ ).

#### IV. DISCUSSION

In this retrospective study, we investigated pathologic nipple invasion according to the NME-to-nipple distance on breast MRI and assessed survival outcomes after surgical procedures to assist in guiding patient selection for NSM. We found that the rate of pathologic nipple invasion was very low at 6.1% (5 of 82 patients) when NME did not extend to the nipple on breast MRI. Furthermore, the rate of pathologic nipple invasion was similarly low at 7.5% (4 of 53 patients) even when limited to patients with the NME-to-nipple distance less than 2 cm. In contrast, pathologic nipple invasion was observed in 53% of patients with NME extension to the nipple. These results suggest that it is difficult to perform NSM when NME extends to the nipple; however, NSM is possible if NME does not involve the nipple on breast MRI.

The nipple-areolar complex involvement in breast cancer is an important issue for the oncologic safety of NSM. Therefore, it is important to identify predictive factors for nipple invasion in order to select patients eligible for NSM. In this study, NME extension to the nipple on preoperative breast MRI was the independent clinicopathologic risk factor for predicting nipple invasion. Slightly more than half of the patients with NME extension to the nipple on breast MRI had nipple invasion on pathologic evaluations in our study. Previous study reported that the protocol of pathologic evaluation of the nipple-areolar complex plays a major role in determining the incidence of nipple involvement<sup>18</sup>. Considering that the incidence of the pathologic invasion is about 50%

even though no pathologic evaluation with serial sections of the entire nipple-areolar complex has been performed in patients with NME extension to the nipple, the actual pathologic invasion rate is expected to be higher when the serial sections evaluation is performed. Further studies are needed to precisely analyze the positive predictive value of NME extension to the nipple on breast MRI.

Notably, the short distance from the tumor to nipple has been known as a critical risk factor for nipple invasion on pathologic evaluation. However, to date, there has been no consensus on which imaging modality is the best option for identifying nipple invasion<sup>19,20</sup>, and the ideal cut-off value of the tumor-to-nipple distance to preserve oncologic safety in patients who receive NSM is also unknown<sup>12,14,21-23</sup>. Furthermore, little is known about the relationship between the NME-to-nipple distance on breast MRI and nipple invasion on pathologic evaluation. In this study, pathologic nipple invasion was actually low as 7.5% even when limited to patients with the NME-to-nipple distance less than 2 cm on breast MRI. Moreover, the risk for pathologic nipple invasion in patients with the NME-to-nipple distance less than 2 cm was not different compared with those with the NME-to-nipple distance 2 cm or more.

In addition, recurrence or death was not noted in patients who underwent NSM for approximately 4 years. Furthermore, there was no difference in survival outcome between NSM and conventional TM/SSM in patients with the NME-to-nipple distance less than 2 cm on breast MRI. These results are in line with those of previous meta-analyses that did not

detect adverse oncologic outcomes of NSM compared with modified radical mastectomy or SSM<sup>24</sup>. A recent study represented that intraoperative frozen section examination of sub-areolar margin was accurate to predict nipple invasion because the false-negative rate was less than 5.0%<sup>25</sup>. Therefore, NSM together with intraoperative frozen examination could be considered when NME does not extend to the nipple on breast MRI.

Although it was not significant in the multivariable analysis, the patients with pathologic nipple invasion tended to be high histologic grade, ER negative, PR negative, and HER2 positive in this analysis. Similarly, several previous studies described that high tumor burden such as large tumor size, lymph node metastasis, and worse molecular characteristics, including high histologic grade, ER negativity, PR negativity, and HER2 positivity, are associated with pathologic nipple invasion, besides the tumor-to-nipple distance<sup>26-28</sup>. Hence, whether to implement NSM in patients with these risk factors related to pathologic nipple invasion should be carefully decided.

This study has several limitations. First, it was a retrospective study from a single institution with a relatively small cohort because we included patients who received upfront breast surgery with NME in the sub-areolar region on breast MRI. Particularly, only 30 patients underwent NSM. Second, the patients who underwent NSM had better molecular characteristics than those who underwent conventional TM or SSM. This imbalance could interfere with the exact assessment of survival outcomes.

Further studies with a larger cohort are needed. Another limitation is that the method of pathologic evaluation to identify the nipple invasion differed according to the surgical procedure. In addition, the accuracy of pathologic nipple invasion could be compromised because the serial sagittal section of the whole nipple-areolar complex was not performed in this study. Despite these limitations, this study had the advantage of analyzing the eligibility for NSM according to NME on preoperative breast MRI.

## **V. CONCLUSION**

The rates of pathologic nipple invasion were low when NME did not extend to the nipple on preoperative breast MRI, although about half of the patients with NME extension to the nipple on breast MRI had pathologic nipple invasion. Accordingly, NSM is an acceptable procedure, although the NME-to-nipple distance on breast MRI is close in properly selected patients who do not have evidence of direct nipple-areolar complex involvement.

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## APPENDICES

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**Availability of data and materials:** The dataset generated and analyzed during

## Supplement Data

Table 1. Baseline Characteristics of the Patients According to Surgical Procedure

|   | TM or SSM (n = 107) | NSM (n = 30) <sup>a</sup> | Total (N = 137) | P     |
|---|---------------------|---------------------------|-----------------|-------|
| Age, median (range)                         | 52 (22-78)          | 44 (24-63)                | 50 (22-78)      | .001  |
| NME size, cm, ± SD                          | 4.01 ± 2.04         | 4.35 ± 1.72               | 4.14 ± 1.97     | .51   |
| DCIS size, cm, ± SD                         | 3.97 ± 2.18         | 2.84 ± 1.22               | 3.72 ± 2.06     | .008  |
| Invasive cancer size, cm, ± SD <sup>b</sup> | 2.14 ± 1.81         | 1.90 ± 0.97               | 2.09 ± 1.68     | .562  |
| NME-to-nipple distance, cm, ± SD            | 0.78 ± 1.048        | 1.91 ± 1.12               | 1.03 ± 1.15     | <.001 |
| HG, <sup>b</sup> n (%)                      |                     |                           |                 | .658  |
| 1 or 2                                      | 19 (65.5)           | 15 (71.4)                 | 34 (68.0)       |       |

|                       |           |           |            |                   |
|-----------------------|-----------|-----------|------------|-------------------|
| <b>3</b>              | 10 (34.5) | 6 (28.6)  | 16 (32.0)  |                   |
| <b>LVI, n (%)</b>     |           |           |            | .83               |
| <b>Positive</b>       | 23 (21.5) | 7 (23.3)  | 30 (21.9)  |                   |
| <b>Negative</b>       | 84 (78.5) | 23 (76.7) | 107 (78.1) |                   |
| <b>T stage, n (%)</b> |           |           |            | .205 <sup>c</sup> |
| <b>0</b>              | 17 (15.9) | 9 (30.0)  | 26 (19.0)  |                   |
| <b>1</b>              | 54 (50.5) | 11 (36.7) | 65 (47.4)  |                   |
| <b>2</b>              | 31 (29.0) | 10 (33.3) | 41 (29.9)  |                   |
| <b>3</b>              | 5 (4.7)   | 0         | 5 (3.6)    |                   |
| <b>N stage, n (%)</b> |           |           |            | .463 <sup>c</sup> |
| <b>0</b>              | 76 (71.0) | 21 (70.0) | 97 (70.8)  |                   |
| <b>1</b>              | 15 (14.0) | 7 (23.3)  | 22 (16.1)  |                   |
| <b>2</b>              | 6 (5.6)   | 0         | 6 (4.4)    |                   |
| <b>3</b>              | 10 (9.3)  | 2 (6.7)   | 12 (8.8)   |                   |
| <b>Stage, n (%)</b>   |           |           |            | .016              |
| <b>0</b>              | 17 (15.9) | 9 (30.0)  | 26 (19.0)  |                   |
| <b>1</b>              | 47 (43.9) | 6 (20.0)  | 53 (38.7)  |                   |
| <b>2</b>              | 26 (24.3) | 13 (43.3) | 39 (28.5)  |                   |
| <b>3</b>              | 17 (15.9) | 2 (6.7)   | 19 (13.9)  |                   |
| <b>ER, n (%)</b>      |           |           |            | .018              |
| <b>Positive</b>       | 73 (68.2) | 27 (90.0) | 100 (73.0) |                   |
| <b>Negative</b>       | 34 (31.8) | 3 (10.0)  | 37 (27.0)  |                   |
| <b>PR, n (%)</b>      |           |           |            | .027              |
| <b>Positive</b>       | 58 (54.2) | 23 (76.7) | 81 (59.1)  |                   |
| <b>Negative</b>       | 49 (45.8) | 7 (23.3)  | 56 (40.9)  |                   |
| <b>HER2, n (%)</b>    |           |           |            | .034              |

|                        |           |           |                   |
|------------------------|-----------|-----------|-------------------|
| <b>Positive</b>        | 44 (41.1) | 6 (20.0)  | 50 (36.5)         |
| <b>Negative</b>        | 63 (58.9) | 24 (80.0) | 87 (63.5)         |
| <b>Subgroup, n (%)</b> |           |           | .081 <sup>§</sup> |
| <b>HR+HER2-</b>        | 56 (52.3) | 23 (76.7) | 79 (57.7)         |
| <b>HR+HER2+</b>        | 17 (15.9) | 4 (13.3)  | 21 (15.3)         |
| <b>HR-HER2+</b>        | 27 (25.2) | 2 (6.7)   | 29 (21.2)         |
| <b>TNBC</b>            | 7 (6.5)   | 1 (3.3)   | 8 (5.8)           |
| <b>Ki-67, n (%)</b>    |           |           | .03               |
| <b>&lt;14</b>          | 51 (47.7) | 21 (70.0) | 72 (52.6)         |
| <b>≥14</b>             | 56 (52.3) | 9 (30.0)  | 65 (47.4)         |

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HG = histologic grade; IR = immediate reconstruction; LVI = lymphovascular invasion; MRI = magnetic resonance image; NME = non-mass enhancement; NSM = nipple-sparing mastectomy; PR = progesterone receptor; SD = standard deviation; SSM = skin-sparing mastectomy; TM = total mastectomy; receptor; TNBC = triple negative breast cancer.

<sup>a</sup>: In 1 patient, the pathologic result was changed from no tumor cell in the subareolar margin on intraoperative frozen section to the presence of tumor cell on the final pathologic report. Finally, excision of the nipple-areolar complex was performed.

<sup>b</sup>: Missing values.

<sup>c</sup>: Fisher exact test.

Table 2. Baseline Characteristics of the Patients According to Nipple Invasion on Pathologic Evaluation

|                            | <b>Pathology(-) (n = 103)</b> | <b>Pathology(+) (n = 34)</b> | <b>Total (N = 137)</b> | <b>P</b> |
|----------------------------|-------------------------------|------------------------------|------------------------|----------|
| <b>Age, median (range)</b> | 49 (24-78)                    | 53 (22-69)                   | 50 (22-78)             | .076     |
| <b>NME size, cm, ± SD</b>  | 4.01 ± 1.99                   | 4.53 ± 1.89                  | 4.136 ± 1.97           | .181     |
| <b>DCIS size, cm, ± SD</b> | 3.67 ± 2.18                   | 3.89 ± 1.64                  | 3.72 ± 2.06            | .592     |

|   |             |                      |             |                   |
|---|-------------|----------------------|-------------|-------------------|
| <b>Invasive cancer size, cm, ± SD<sup>a</sup></b> | 2.24 ± 1.77 | 1.96 ± 1.33          | 2.16 ± 1.67 | .457              |
| <b>NME to nipple distance, cm, ± SD</b>           | 1.30 ± 1.18 | 0.221 ± 0.57         | 1.03 ± 1.15 | <.001             |
| <b>HG,<sup>a</sup> n (%)</b>                      |             |                      |             | .007              |
| <b>1 or 2</b>                                     | 59 (74.7)   | 12 (46.2)            | 71 (67.6)   |                   |
| <b>3</b>  | 20 (25.3)   | 14 (53.8)            | 34 (32.4)   |                   |
| <b>LVI, n (%)</b>                                 |             |                      |             | .089              |
| <b>Positive</b>                                   | 19 (18.4)   | 11 (32.4)            | 30 (21.9)   |                   |
| <b>Negative</b>                                   | 84 (81.6)   | 23 (67.6)            | 107 (78.1)  |                   |
| <b>TM method, n (%)</b>                           |             |                      |             | .007              |
| <b>Conventional</b>                               | 49 (47.6)   | 20 (58.8)            | 69 (50.4)   |                   |
| <b>NSM</b>  | 29 (28.2)   | 1 <sup>b</sup> (3.0) | 30 (21.9)   |                   |
| <b>SSM</b>  | 25 (24.3)   | 13 (38.2)            | 38 (27.7)   |                   |
| <b>IR, n (%)</b>                                  |             |                      |             | .401              |
| <b>Yes</b>  | 57 (55.3)   | 15 (44.1)            | 72 (52.6)   |                   |
| <b>No</b>   | 46 (44.7)   | 19 (55.9)            | 65 (47.4)   |                   |
| <b>T stage, n (%)</b>                             |             |                      |             | .620 <sup>c</sup> |
| <b>0</b>  | 19 (18.4)   | 7 (20.6)             | 26 (19.0)   |                   |
| <b>1</b>  | 48 (46.6)   | 17 (50.0)            | 65 (47.4)   |                   |
| <b>2</b>  | 31 (30.1)   | 10 (29.4)            | 41 (29.9)   |                   |
| <b>3</b>  | 5 (4.9)     | 0                    | 5 (3.6)     |                   |
| <b>N stage, n (%)</b>                             |             |                      |             | .975              |
| <b>0</b>  | 73 (70.9)   | 24 (70.6)            | 97 (70.8)   |                   |
| <b>≥1</b>   | 30 (29.1)   | 10 (29.4)            | 40 (29.2)   |                   |
| <b>Stage, n (%)</b>                               |             |                      |             | .435              |
| <b>0</b>  | 19 (18.4)   | 7 (20.6)             | 26 (19.0)   |                   |

|                        |           |           |            |
|------------------------|-----------|-----------|------------|
| <b>1</b>               | 38 (36.9) | 15 (44.1) | 53 (38.7)  |
| <b>2</b>               | 33 (32.0) | 6 (17.6)  | 39 (28.5)  |
| <b>3</b>               | 13 (12.6) | 6 (17.6)  | 19 (13.9)  |
| <b>ER, n (%)</b>       |           |           | .089       |
| <b>Positive</b>        | 79 (76.7) | 21 (61.8) | 100 (73.0) |
| <b>Negative</b>        | 24 (23.3) | 13 (38.2) | 37 (27.0)  |
| <b>PR, n (%)</b>       |           |           | .004       |
| <b>Positive</b>        | 68 (66.0) | 13 (38.2) | 81 (59.1)  |
| <b>Negative</b>        | 35 (34.0) | 21 (61.8) | 56 (40.9)  |
| <b>HER2, n (%)</b>     |           |           | .022       |
| <b>Positive</b>        | 32 (31.1) | 18 (52.9) | 50 (36.5)  |
| <b>Negative</b>        | 71 (68.9) | 16 (47.1) | 87 (63.5)  |
| <b>Subgroup, n (%)</b> |           |           | .021       |
| <b>HR+HER2-</b>        | 63 (61.2) | 16 (47.1) | 79 (57.7)  |
| <b>HR+HER2+</b>        | 16 (15.5) | 5 (14.7)  | 21 (15.3)  |
| <b>HR-HER2+</b>        | 16 (15.5) | 13 (38.2) | 29 (21.2)  |
| <b>TNBC</b>            | 8 (7.8)   | 0         | 8 (5.8)    |
| <b>Ki-67</b>           |           |           | .125       |
| <b>&lt;14</b>          | 58 (56.3) | 14 (41.2) | 72 (52.6)  |
| <b>≥14</b>             | 45 (43.7) | 20 (58.8) | 65 (47.4)  |

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HG, histologic grade; IR, immediate reconstruction; LVI, lymphovascular invasion; MRI, magnetic resonance image; NME, non-mass enhancement; NSM, nipple-sparing mastectomy; PR, progesterone receptor; SD, standard deviation; SSM, skin-sparing mastectomy; TM, total mastectomy; TNBC, triple negative breast cancer.

<sup>a</sup>: Missing values.

<sup>b</sup>: In this patient, the pathologic result was changed from no tumor cell in the subareolar margin on intraoperative frozen section to the presence of tumor cell on the final pathologic report. Finally, excision of the nipple-areolar complex was performed.

<sup>c</sup>: Fisher exact test.

유두 보존 유방 절제술 시행을 위한 수술 전 자기공명 영상 상의  
유두 밑 비종괴 조영 증강의 의의  
<지도교수 정준 >

연세대학교 대학원 의학과  
전시열

유방암 환자들의 유방 자기공명영상(MRI) 에서 유두 밑 비종괴조영 증강(Non-mass Enhancement, NME) 존재 시 유두보존 유방절제술 (Nipple sparing mastectomy, NSM) 의 실행가능성은 명확하지 않다. 이 연구는 수술 전 유방 MRI 에서 NME-유두 거리에 따라 NSM의 적격성을 평가하고 한다.

대상과 방법: 수술 전 유방암을 진단받고 유방 MRI 촬영 시 NME가 존재하며 유방 절제술을 받은 유방암 환자를 확인 하였다. 유두 침윤의 발생률을 유방 MRI에서의 NME- 유두 거리에 따라 병리학 적으로 평가하고, 병리학적 유두 침습과 관련된 임상병리학 적 인자를 분석 하였다.

결과: 137 명의 환자 중 55 명 (40.1 %)이 NME의 유두 침범이 있었고, 53 명(38.7 %)이 NME-유두 거리가 2cm 미만이며, 29 명 (21.2 %)이 2cm 이상의 NME-유두 거리를 가졌다. NME가 유두로 침범한 환자에서 유두의 병리학적 악성 비율은 52.7 % 이고, NME-유두 거리가 2cm 미만인 환자의 경우 7.5 %, NME-유두 간격이 2cm 이상인 환자에서는 3.4 % 를 보였다. ( $P < .001$ ) 유두로의 NME 확장은 병리학적 유두 악성율에 대한 독립적인 위험 인자였다 (odds ratio: 21.702; 95 % 신뢰 구간, 2.613-180.225;  $P = .004$ ).

수술 후 생존율을 분석하였을 때, NME-유두 거리가 2cm 미만인 환자에서 유두보존 유방절제술과 기존의 유방 절제술 / 피부 보존 유방 절제술 사이의 결과는 다르지 않았다.

결론 : 수술 전 유방 MRI 상 NME의 유두 침습이 없을 경우 유두 보존 유방절제술은 가능 할 수 있다.

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핵심되는 말: 유방암, 비종괴조영증강, 유방 자기공명영상, 유방절제술, 유두

## PUBLICATION LIST

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