ORIGINAL ARTICLE

A novel nipple–areola complex involvement predictive index for indicating nipple-sparing mastectomy in breast cancer patients

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Abstract

Background Nipple-sparing mastectomy (NSM) is increasingly used in breast cancer patients, as it offers better cosmetic outcomes and improves quality of life. Nipple–areola complex (NAC) involvement must be accurately determined to identify which patients may be candidates for NSM. We aimed to identify the predictors of NAC involvement and develop a clinical predictive model to determine the patients for whom NAC preservation may be considered.

Patients and methods Patients ($n = 168$) with primary operable breast cancer who underwent subcutaneous mastectomy for breast reconstruction at Saitama Medical Center from July 2013 to December 2017 were selected from the hospital's surgical database.

Results The clinicopathological factors of tumor size $\geq$ 4 cm ($p < 0.001$), nipple-to-tumor distance (NTD) < 1 cm by mammography ($p = 0.002$), NTD < 1 cm by magnetic-resonance imaging (MRI) ($p < 0.001$), nipple contrast findings by MRI ($p < 0.001$), tumor in central portion ($p < 0.001$), multicentric/focal lesion ($p < 0.001$), and clinical node involvement ($p = 0.014$) were significantly associated with the presence of NAC involvement. Each predictor was scored 0 or 1. A score of 0–3 points was defined as low risk, 4 points as intermediate risk, and 5–7 points as high risk. Using these classification criteria, NAC involvement rate was determined to be 3.5% in low-risk, 68.7% in intermediate-risk, and 90.0% in high-risk specimens. A significant correlation was observed between the risk group and NAC involvement ($p < 0.001$).

Conclusion This nipple–areola complex involvement predictive index can be used to determine the appropriate indication for NSM in breast cancer patients who request NAC preservation with more oncological safety.

Keywords Breast cancer · Breast reconstruction · Nipple–areolar complex involvement · Nipple-sparing mastectomy · Sub-nipple biopsy

Introduction

In the past several decades, the principles of surgical management of breast cancer have changed remarkably. While breast cancer is often associated with systemic involvement at the time of diagnosis, the surgical management of breast cancer has become more conservative. Although breast-conserving surgery followed by radiation therapy has been established as a standard treatment for breast cancer, patients who have wider intraductal compartments, large tumors, and multicentric or multifocal diseases are ineligible for this treatment option [1, 2].

Recently, immediate breast reconstruction has become the standard treatment for some women who require a mastectomy and choose breast-preservation treatments. In skin-sparing mastectomy (SSM), which involves the removal of

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the nipple–areola complex (NAC) and mammary gland, preservation of the skin overlying/enveloping the breast permits immediate breast reconstruction, minimizes deformity, and improves cosmetic outcomes [3–5]. SSM was first described by Toth and Lappert in 1991 [6]. Although SSM showed remarkable aesthetic reconstruction outcomes, a number of studies have raised concerns regarding the oncological safety of this procedure [7–9].

More recently, to decrease the psychological impact of mutilation, the conservation of the NAC has been proposed [10, 11]. Although NAC preservation increases the risk of local recurrences in the retroareolar glandular tissue, it helps patients feel less mutilated, as it preserves an important part of their breast identity [12]. Therefore, nipple-sparing mastectomy (NSM) is increasingly used in patients with breast cancer, as it offers better cosmetic outcomes and improves patients' quality of life [10, 13, 14]. NSM is currently considered as a possible alternative to SSM in selected breast cancer patients undergoing immediate breast reconstruction [15, 16], and the oncological safety of NSM is supported by some retrospective [13, 17] and prospective clinical data [11]. The previous studies have shown that the incidence of occult malignant invasion of the clinically normal nipple in mastectomy specimens ranged from 0 to 58% [13, 18–21], which means that there is a potential risk of leaving an occult tumor within that nipple with NSM. Accurately predicting tumor involvement in the NAC is necessary to determine which patients may be candidates for NSM [22].

The characteristics associated with NAC involvement are tumor size, nipple-to-tumor distance (NTD), multicentricity/focality, and node metastasis [16]. NTD has been advocated by Loewen et al. [23] and Yamashiro et al. [24] as a better predictor of NAC involvement. However, in most cases, the margins of the cancer are difficult to evaluate clinically. In addition, the previous studies have reported predictive formulas for NAC involvement; however, these criteria were either not available before surgery or not reliable because of differences in methodology [23, 25].

Intraoperative sub-nipple biopsy, which involves the collection of tissues from beneath the NAC for frozen sections, is performed to detect occult nipple invasion and allows for immediate resection of the NAC during mastectomy if biopsy specimens show evidence of tumor involvement [11, 26, 27]. The sensitivity and specificity of sub-nipple biopsy in detecting malignant cells in the retroareolar region ranged from 38.5 to 90.9% and from 91.7 to 100%, respectively [11, 17, 28–35].

While the surgeon's primary responsibility is the safe removal of the cancer, it is also important to preserve quality of life and minimize psychological damage to the patient. This study aimed to identify the predictors of NAC involvement and develop a clinical predictive model to determine the patients who can safely undergo NAC preservation.

Patients and methods

Patients

A total of 168 patients with primary operable breast cancer who underwent subcutaneous mastectomy for breast reconstruction at Saitama Medical Center from July 2013 to December 2017 were selected from the hospital's surgical database. Patients who were indicated for subcutaneous mastectomy for breast reconstruction underwent preoperative mammography (MMG), ultrasonography (US), and magnetic-resonance imaging (MRI). Tumor size was measured by US and MRI, and NTD was measured by MMG and MRI. All patients who received neoadjuvant chemotherapy were evaluated on the basis of the findings of diagnostic imaging studies performed before starting systemic therapy.

Surgical procedure

Diagnostic imaging was used to determine patients who were candidates for NAC preservation. During the course of NSM, NAC involvement was verified by intraoperative sub-nipple biopsy; if tumor involvement was suspected, SSM or areolar-sparing mastectomy (ASM) was performed.

Sub-nipple biopsy

In our study, NAC involvement was defined by the presence of invasive carcinoma and/or ductal carcinoma in situ at the subareolar margin. Tissue specimens from beneath the NAC were obtained, freeze-sectioned, and then evaluated intraoperatively. If the sub-nipple frozen section revealed malignant findings intraoperatively during NSM, the surgical procedure was converted to NAC resection.

Statistical analysis

Statistical analysis was performed using the SPSS 23.0 statistical software (SPSS Inc., Chicago, IL, USA). The clinicopathological variables were compared using Fisher's exact test and a Chi-square test. A p value lower than 0.05 was considered significant. Receiver operating characteristic (ROC) curves were constructed for significant variables to detect the best cutoff points for distinguishing between cases and controls.

Results

Patients' characteristics

A total of 168 primary breast cancer patients who underwent subcutaneous mastectomy were included in this study. The

median age at diagnosis was 48 years (range 33–80 years); 33.3% (56/168) of the patients were postmenopausal women and 32.1% (54/168) had stage 0 cancer. Of the 168 patients, 133 experienced invasive carcinomas; of them, 87.2% (116/133) were estrogen receptor positive, 78.2% (104/133) were progesterone receptor positive, and 1.5% (2/133) were human-epidermal growth factor receptor 2 positive. A total of 162 patients underwent axilla lymph node surgery; of them, 23.4% (38/162) were positive for pathological nodes and 11.3% (19/168) received neoadjuvant chemotherapy. Of the 168 patients, 140 (76.2%) underwent intraoperative sub-nipple biopsy and 98.8% (166/168) underwent breast reconstruction. NSM was indicated in 88.1% (148/168) of patients, while SSM or ASM was indicated in 11.9% (20/168) of patients preoperatively. Of the 148 patients who underwent NSM, 8.1% (12/148) were converted to SSM or ASM intraoperatively. Among 166 patients who underwent breast reconstruction, 40.4% (67/166) of patients underwent breast reconstruction with an implant, 12.6% (21/166) with the latissimus dorsi, and 47.0% (78/166) with tissue expanders (Table 1).

Correlation between selected surgical procedures and NAC involvement in permanent pathological specimens

Of the 148 patients with preserved NAC, 89.9% (133/148) were negative and 10.1% (15/148) were positive for NAC involvement in permanent pathological specimens. Of the 20 patients who underwent NAC resection, only 50.0% (10/20) had NAC involvement. This revealed NAC involvement with a sensitivity of 40.0%, a specificity of 93.0%, a PPV of 50.0%, and an NPV of 89.9% (Table 2).

Correlation between sub-nipple frozen section biopsy specimens and definitive pathological results of NAC involvement in NSM

Of the 140 patients who underwent intraoperative sub-nipple frozen section biopsy, 19.3% (27/140) showed NAC involvement and 80.7% (113/140) showed the absence of NAC involvement. A significant correlation was observed between the results of the intraoperative sub-nipple biopsy and definitive pathologic results of NAC involvement, with a sensitivity of 93.3%, a specificity of 89.6%, a PPV of 51.9%, and an NPV of 99.1% ($p < 0.001$) (Table 3).

Correlation between NAC involvement and clinicopathological factors

Statistical analysis revealed that tumor size ≥ 4 cm by MRI ($p < 0.001$), NTD < 1 cm by MMG ($p = 0.002$), NTD < 1 cm by MRI ($p < 0.001$), NAC contrast findings by

Table 1 Patients' characteristics

	No. of patients	%
Age (years), median (range)	48 (33–80)	
Menopausal status		
Premenopausal	112	66.7
Postmenopausal	56	33.3
BMI, median (range)	21.3 (15.5–41.6)	
Tumor size (cm), median (range) by US	1.8 (0–12.5)	
NTD by MMG		
< 1 cm	42	26.0
≧ 1 cm	104	61.9
Unknown	22	13.1
Tumor size (cm), median (range), MRI	2.3 (0–7)	
NTD by MRI		
< 1 cm	33	19.6
≧ 1 cm	121	72
Unknown	14	8.4
MRI NAC enhancement		
Negative	127	75.6
Positive	26	15.5
Unknown	15	8.9
Multicentric/focal		
No	144	85.7
Yes	24	14.3
Tumor location		
Peripheral	108	64.3
Central	60	35.7
Primary tumor size (T)		
Is	54	32.0
1	52	31.0
2	52	31.0
3	9	5.4
4	1	0.6
Pathological node status (N)		
Negative	148	88.1
Positive	20	11.9
Stage at the time of diagnosis		
0	54	32.1
1	51	30.8
2a	37	22.0
2b	22	13.1
3a	3	1.8
3b	1	0.6
Permanent pathology		
DCIS	34	20.2
LCIS	1	0.6
IDC	123	73.2
ILC	10	6.0
ER		
Negative	17	12.8
Positive	116	87.2
PgR		
Negative	29	21.8
Positive	104	78.2

Table 1 (continued)

	No. of patients	%
HER2		
Negative	131	98.5
Positive	2	1.5
Ki-67		
<20%	46	34.6
≧20%	87	65.4
Nuclear grade		
1	87	65.4
2	32	24.1
3	11	8.3
Unknown	3	2.3
Lymph invasion (ly)		
No	78	46.4
Yes	79	47.1
Unknown	11	6.5
Vascular invasion (v)		
No	131	78.0
Yes	25	14.9
Unknown	12	7.1
Pathological node status (n)		
0	124	76.5
1–3	30	18.5
4	4	4.9
Subcutaneous mastectomy		
NSM	136	81.0
NSM→SSM or ASM	12	7.2
SSM or ASM	20	11.8
Axillary lymph node dissection		
SLNB	122	72.6
SLNB→Ax	22	13.1
Ax	14	8.3
None	10	6.0
Breast reconstruction		
IMP	67	39.9
LD	21	12.5
TE	78	46.4
Sub-nipple biopsy		
No	48	23.8
Yes	140	76.2
Neoadjuvant chemo Tx		
No	149	88.7
Yes	19	11.3
Nipple necrosis		
No	162	96.4
Yes	6	3.6

BMI body mass index, *NTD* nipple-to-tumor distance, *MMG* mammography, *MRI* magnetic-resonance imaging, *ER* estrogen receptor, *PgR* progesterone receptor, *HER2* human-epidermal growth factor receptor 2, *NSM* nipple-sparing mastectomy, *SSM* skin-sparing mastectomy, *ASM* areolar-sparing mastectomy, *SLNB* sentinel lymph node biopsy, *Ax* axillary lymph node dissection, *IMP* implant, *LD* latissimus dorsi, *TE* tissue expander

Table 2 Correlation between selected surgical procedures and NAC involvement in permanent pathological specimens

		Actual NAC involvement		
		Positive	Negative	
Predictive NAC involvement	Positive (NAC resection)	10	10	20
	Negative (NAC preservation)	15	133	148
p < 0.001		25	143	168

Sensitivity 40.0%, specificity 93.0%, PPV 50%, NPV 89.9%, FNR 60.0%, FPR 7.0%, accuracy 85.1%

NAC nipple–areolar complex, *PPV* positive predictive value, *NPV* negative predictive value, *FNR* false-negative rate, *FPR* false-positive rate

Table 3 Correlation between sub-nipple frozen section biopsy specimens and definitive pathologic results of NAC involvement in NSM

		Actual NAC involvement		
		Positive	Negative	
Predictive NAC involvement	Positive (NAC resection)	14	13	27
	Negative (NAC preservation)	1	112	113
p < 0.001		15	125	140

Sensitivity 93.3%, specificity 89.6%, PPV 51.9%, NPV 99.1%, FNR 6.7%, FPR 10.4%, accuracy 90.0%

NAC nipple–areolar complex, *PPV* positive predictive value, *NPV* negative predictive value, *FNR* false-negative rate, *FPR* false-positive rate

MRI ($p < 0.001$), tumor central location ($p < 0.001$), multicentric/focal lesion ($p < 0.001$), clinical node involvement ($p = 0.014$), intraoperative sub-nipple biopsy ($p < 0.001$), vascular invasion ($p = 0.029$), and pathological node involvement ($p < 0.001$) were significantly associated with NAC involvement (Table 4).

Nipple–areola complex involvement predictive index (NACPI)

Among clinicopathological factors that showed significant differences in Fisher's exact test, 7 factors related to preoperative clinical findings were scored with 0 or 1, respectively (Table 5). A total score of 0–3 points was defined as low risk, 4 points as intermediate risk, and 5–7 points as high risk (Fig. 1a). According to this classification, 84.5% (142/168) of patients were low risk, 9.5% (16/168) were intermediate risk, and 6.0% (10/168) were high risk. NAC involvement rates were 3.5% (5/142) in the low-risk group, 68.7% (11/16) in the intermediate-risk group, and 90.0% (9/10) in the high-risk group; a significant correlation was observed between

Table 4 Correlation between NAC involvement and clinicopathological factors

Factor	NAC positive	NAC negative	p value
Menopausal status			1.000
Pre	17	95	
Post	8	48	
Tumor size (US)			1.000
< 4 cm	23	125	
≧ 4 cm	2	13	
Tumor size (MRI)			< 0.001
< 4 cm	3	112	
≧ 4 cm	20	19	
NTD (MMG)			0.002
< 1 cm	13	29	
≧ 1 cm	10	94	
NTD (MRI)			< 0.001
< 1 cm	15	18	
≧ 1 cm	8	113	
NAC contrast finding (MRI)			< 0.001
Negative	6	121	
Positive	17	9	
Tumor location			< 0.001
Peripheral	6	102	
Central	19	41	
Multicentric/focal			< 0.001
No	14	130	
Yes	11	13	
c(N)			0.014
Negative	18	130	
Positive	7	13	
Neoadjuvant chemotherapy			0.167
No	20	129	
Yes	5	14	
Pathology			0.648
Invasive	18	93	
Non-invasive	7	50	
Intraoperative sub-nipple biopsy			< 0.001
Negative	1	112	
Positive	14	13	
ER			0.074
Negative	0	17	
Positive	20	96	
PgR			0.242
Negative	2	27	
Positive	18	86	
HER2			1.000
Negative	20	112	
Positive	0	2	

Table 4 (continued)

Factor	NAC positive	NAC negative	p value
ly			0.08
0	8	70	
1	17	62	
v			0.029
0	16	115	
1	8	17	
p(n)			< 0.001
No	10	114	
Yes	15	23	
Ki-67			0.446
< 20%	5	41	
≧ 20%	15	72	
Nuclear grade			0.213
1 or 2	20	99	
3	0	11	

NAC nipple–areolar complex, *BMI* body mass index, *NTD* nipple-to-tumor distance, *MMG* mammography, *MRI* magnetic-resonance imaging, *ER* estrogen receptor, *PgR* progesterone receptor, *HER2* human-epidermal growth factor receptor 2

Table 5 Nipple–areolar complex involvement predictive index

Predictor	0	1	
Tumor size	< 4 cm	≧ 4 cm	
NTD (MMG)	≧ 1 cm	< 1 cm	
NTD (MRI)	≧ 1 cm	< 1 cm	
NAC enhancement (MRI)	No	Yes	
Tumor location	Peripheral	Central	
Multicentric/focal	No	Yes	
Clinical node metastasis	No	Yes	
Total score	0–3	4	5–7
Risk	Low	Intermediate	High

NAC nipple–areolar complex, *MMG* mammography, *MRI* magnetic-resonance imaging, *NTD* nipple–tumor distance

the risk group and NAC involvement ($p < 0.001$) (Fig. 1b). Furthermore, assuming that NAC was preserved for low-risk patients and resected for intermediate-risk and high-risk patients, NAC involvement was verified using the NACPI (sensitivity: 80.0%, specificity: 95.8%, PPV: 76.9%, and NPV: 96.5%; AUC 0.879, 95% CI 0.784–0.974) (Table 6, Fig. 1c). This study showed that the NACPI contributed to improving the accuracy of selecting the appropriate surgical procedure for breast cancer patients (Fig. 1d).
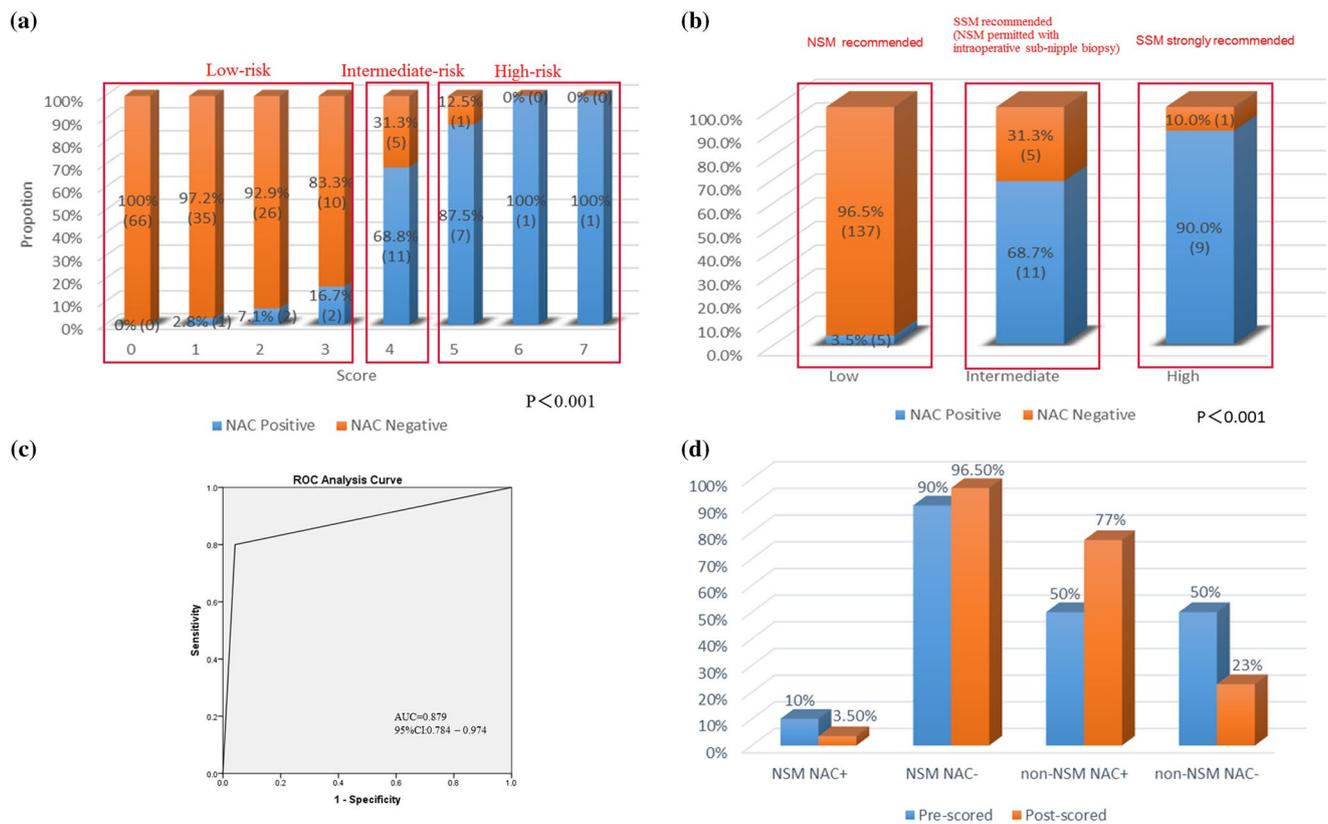
(a)

(b)

(c)

(d)

Fig. 1 Nipple–areola complex involvement predictive index (NACPI). **a** Correlation between categorized risk groups and NAC involvement rate. **b** Recommendation of surgical procedures based on the NACPI. **c** Receiver operating characteristic curve analysis. **d** Improved accuracy of NAC involvement rate in each surgical procedure by the NACPI

Table 6 Correlation between predictive NAC involvement by NACPI and pathologic results

		Actual NAC involvement		
		Positive	Negative	
Predictive NAC involvement	Positive (NAC resection)	20	6	26
	Negative (NAC preservation)	5	137	142
$p < 0.001$		25	143	168

Sensitivity 80.0%, specificity 95.8%, PPV 76.9%, NPV 96.5%, FNR 20%, FPR 4.2%, accuracy 93.5%

NAC nipple–areolar complex, *PPV* positive predictive value, *NPV* negative predictive value, *FNR* false-negative rate, *FPR* false-positive rate

Discussion

With improved long-term survival rates, many breast cancer patients have required more conservative surgical options, as the focus has shifted from concerns about life expectancy rates to concerns regarding postoperative cosmetic outcomes. Before NAC preservation became a viable option in carefully selected patients, SSM with breast reconstruction was the primary method of improving cosmetic outcomes. To evaluate the oncological safety of performing NAC-sparing procedures, several retrospective studies have examined the frequency of occult malignant involvement of the NAC. These previous studies have shown that the incidence of occult malignant invasion of the clinically normal nipple in mastectomy specimens ranged from 0 to 58% [13, 18–21], which means that there is a potential risk of leaving an occult tumor within that nipple when preserving the NAC.

Of the 148 patients who underwent NSM in this study, 89.9% (133/148) were negative for NAC involvement in permanent pathological specimens, a result which was comparable to those of the previous studies [31]. Of the 20 patients who were offered NAC resection due to suspicion of preoperative NAC involvement, NAC positivity in permanent pathological specimens was only 50% (10/20). In other words, half of the patients who were offered NAC resection had false-positive results and NAC resection was not necessary. These findings suggest that there is a possibility of overestimating NAC involvement by preoperative radiology.

Various sub-nipple frozen biopsy techniques have been described, and most involve collection of tissues from below the nipple, freezing it at low temperatures, sectioning the specimen, and then examining it during the operation [26, 27, 33]. However, none of the methods have been standardized, resulting in a wide range of false-negative rates (1.2–23.1%) [11, 17, 28–36]. In this study, sub-nipple biopsy was significantly associated with NAC involvement, with a sensitivity of 93.3%, a specificity of 89.6%, a PPV of 51.9%, an NPV of 99.1%, a false-negative rate (FNR) of 6.7%, a false-positive rate (FPR) of 10.4%, and an overall accuracy rate of 90.0%. One patient who had false-negative results showed a wide range of polymorphic segmental microcalcifications on MMG. Overall, our results are comparable with those reported in the previous studies, indicating that intraoperative sub-nipple biopsy is a reliable method for detecting cancer invasion into the NAC.

The National Comprehensive Cancer Network guideline suggests that it is necessary to evaluate the tissue beneath the NAC; however, the previous literature indicated that preoperative MRI evaluation of NAC involvement without intraoperative sub-nipple biopsy is sufficient to detect NAC involvement, and this method is more cost-effective [36]. In this study, almost all NSM patients underwent intraoperative sub-nipple biopsy, but this may not be necessary in low-risk patients, such as those with small tumor size, large NTD, peripheral tumors, no enhancement under the nipple, and no clinical lymph node metastasis on radiology.

Tumor size and NTD have been correlated with NAC involvement. Lambert et al. reported that larger tumor size is associated with increasing incidence of NAC involvement, particularly if it is > 4 cm in diameter [37]. Lagios et al. also reported that NAC involvement was extremely rare when the NTD was > 2.5 cm [38]. These reports suggest that the use of both size and distance in predictive models may further improve accurate indications of nipple–areolar involvement.

In a recent study, Schecter et al. proposed an NAC involvement scoring system [25]. This was found to predict NAC involvement with a sensitivity of 92%, a specificity of 77%, an NPV of 93%, and an AUC value of 0.94 (95% CI 0.85–1.000) in the ROC analysis curve. The NAC involvement score may be of limited clinical use for preoperative judgment of whether the NAC can be preserved or not, as it contains pathological tumor size and stage. Moreover, the sample size in that study was limited to 31 cases. However, we applied this formula to 168 breast cancer patients in this study, and NAC involvement was predicted with a sensitivity of 86.4%, a specificity of 32.1%, a PPV 17.6%, and an NPV of 93.3%. The AUC [0.553 (95% CI 0.458–0.648) in the ROC analysis curve] was lower than that in their report.

The previous studies have also shown that, besides tumor size and NTD, NAC involvement was significantly associated with tumor central location, multicentricity/focality,

and lymph node metastasis [16, 39, 40], which was consistent with our results. Statistical analysis in this study revealed that tumor size ≧ 4 cm by MRI, NTD < 1 cm by MMG, NTD < 1 cm by MRI, nipple enhancement by MRI, tumor central location, multicentric/focal lesion, clinical node (N) involvement, intraoperative sub-nipple biopsy, vascular invasion, and pathological node (n) involvement were significantly related to NAC involvement, which is consistent with the previous literature. We developed an NAC involvement predictive index using these 7 factors. Each predictor was scored 0 or 1, and the total scores were used to categorize the tumors as low (0–3 points), intermediate (4 points), or high (5–7 points) risk. The NAC involvement rates of the risk groups classified by the NACPI were as follows: 3.5% (5/142) in low-risk patients, 68.7% (11/16) in intermediate-risk patients, and 90.0% (9/10) in high-risk patients. This finding revealed that the NACPI is significantly associated with NAC involvement.

Furthermore, assuming that NAC was preserved in low-risk patients and resected in intermediate- and high-risk patients, the permanent pathological results of NAC involvement improved to a sensitivity of 80.0%, a specificity of 95.8%, a PPV of 76.9%, an NPV of 96.5% and an AUC 0.879 (95% CI 0.784–0.974). Thus, the NACPI improved the accuracy of appropriate surgical procedure selection. In addition, as the NACPI does not use complicated formulas, it is useful for surgeons to instantly evaluate the risk of NAC involvement in the clinical setting.

Neoadjuvant chemotherapy cases comprised 11.3% (19/168) of this study's population. As described in Table 4, there was no significant correlation with NAC involvement in the subgroups of patients with and without neoadjuvant chemotherapy ($p = 0.167$). Therefore, we believe that constructing the NAC predictive model is unlikely to be affected by preoperative systemic therapy if the diagnostic imaging results before starting the systemic therapy are evaluated. Further studies are needed to strictly assess the accuracy of NACPI in patients receiving preoperative systemic therapy.

The benefits of the NACPI were as follows: (1) intraoperative pathology becomes unnecessary for the low-risk group; (2) patients in the intermediate-risk group who wish to undergo NSM can verify the safety of this procedure through intraoperative pathology testing; and (3) it provides a strong basis on which to recommend NAC excision for the high-risk group. Of the 125 patients without NAC involvement on permanent pathology review, the intraoperative sub-nipple biopsy specimens of 112 patients showed the absence of NAC involvement, and 96.4% (108/112) were considered as low risk. These data suggest that intraoperative sub-nipple biopsy can be omitted in low-risk patients by use of the NACPI. In the intermediate-risk group, the NAC-positive rate was 68.7% (11/16). Of these 11 patients, 6 received treatment for NSM. However, as all 6 patients showed NAC

involvement on intraoperative sub-nipple biopsy, NAC resection was performed (Supplementary Table 1). Therefore, intraoperative sub-nipple biopsy may be necessary when NSM is performed in patients with intermediate risk. In contrast, as NAC involvement was found in 90% (9/10) of high-risk patients (total score of 5 or higher), these patients should not undergo NAC-sparing surgeries. Taken together, the data suggest that the NACPI can also be a reliable index to evaluate the necessity of intraoperative sub-nipple biopsy according to the risk.

As NSM patients undergo intraoperative sub-nipple biopsy, and a positive biopsy enables the conversion of NSM to nipple resection, the contribution of the NACPI for the improved detection of NAC involvement is limited. If patients wish to have nipple preservation despite the possibility of NAC involvement as determined by radiological analysis, the NACPI contributes greatly to improved cosmetic and quality-of-life outcomes in such cases. These results suggest that the indication for NSM may be safely expanded to include patients who may have been previously been selected to undergo SSM due to a large tumor size and a short NTD.

Our study may include some biases due to its retrospective nature. Thus, only prospective studies of NAC-sparing mastectomy for breast cancer patients will be able to assess the best parameters to predict NAC involvement, and long-term follow up data will be required to assess the oncological safety of the procedure.

Conclusion

When considering the preservation of the NAC, it is important to perform a comprehensive, preoperative evaluation of tumor diameter, NTD, nipple–areolar contrast findings on MRI, tumor location, presence of multicentricity/focality, and the possibility of lymph node metastasis. The data from this study suggest that the NACPI presented herein can be used by surgeons to determine whether NSM is indicated for breast cancer patients who request NAC preservation with more oncological safety.

Compliance with ethical standards

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