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Prediction of occult nipple-areola complex involvement in breast cancer patients

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The aim of this study was to evaluate predictive factors for the nipple-areola complex (NAC) involvement, and to define a subgroup of patients who may benefit from skin-sparing mastectomy with the NAC preservation in breast cancer patients. Univariate and multivariate analyses were carried out in the retrospective data of 397 eligible patients. The NAC involvement was histopathologically proved in 58 (14.6%) of the patients. In the multivariate logistic regression analysis showed that tumor location (central vs peripheral; p<0.0001; hazard ratio [HR], 7.5; 95% confidence interval [CI], 3.4-14.6), number of positive axillary lymph nodes (≥10 vs <10; p<0.005; HR, 2.9; CI, 1.3-6.1), and lymphatic vascular invasion (yes vs no; p<0.0001; HR, 3.5; CI, 1.7-7.1) were the most important prognostic factors. Whereas patients with 2 or 3 risk factors were accepted as high-risk group for the NAC involvement, those with no or 1 risk factor was defined as low-risk group. These groups had a 50.0% NAC involvement rate and a 8.1% NAC involvement rate, respectively (p<0.0001). In conclusion, this study showed that patients with 2 or 3 predictive factors had a high risk of the NAC involvement. These risk factors should be taken into consideration in patient selection for skin-sparing mastectomy with the NAC preservation.

Key words: nipple-areola complex; involvement; breast cancer; mastectomy.

Skin-sparing mastectomy (SSM) which includes the resection of the nipple-areola complex (NAC) with the breast parenchyma improves the aesthetic outcome for breast cancer patients, and it also compromises the oncological safety [1, 2]. Because of the changing paradigm in breast carcinoma treatment, there is an increasing interest about a less radical but more technically demanding and oncologically tailored breast surgery [2]. In the SSM, the NAC is removed because of the belief that the NAC and its adjacent ducts may contain tumor cells which have spread distally along the ducts from the primary tumor [3]. Recently, a change in the SSM technique with preservation of the NAC named as the NAC-sparing mastectomy has been created, and also shown an equivalent local control of disease [4]. However, few studies have been published on the presence of residual disease in the NAC. Therefore, the criteria of patient selection for the NAC preservation have not been yet defined precisely [5].

The aim of the present study was to evaluate the rate of the NAC involvement in the breast cancer patients and to investigate predictive factors for the NAC involvement based on the clinicopathological features, and to define a subgroup of patients who may be available for SSM with the NAC preservation.

Patients and Methods

In this retrospective cohort study, the charts and final pathological reports of female patients underwent modified radical mastectomy for invasive breast carcinoma, from 1997 to 2004 at our hospital, were reviewed. Clinical lymph node classification and tumor staging were realized according to the American Joint Committee on Cancer criteria [6]. Histologic grading was performed using the criteria of Bloom and Richardson [7]. Lymphatic vascular invasion (LVI) was defined as the presence of tumor emboli in peritumoral lymphatic spaces, capillaries or postcapillary venules. Estrogen and progesteron receptor status were determined by immunohistochemical means on paraffin-embedded tissue and were taken as positive if more than 10% of tumor cells showed staining. Central location for tumor was defined as cylinder of breast tissue beneath the NAC from the dermis to the pectoral fas-

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cia, and peripheral location for tumor was accepted as those out of this area, as indicated previously elsewhere [5].

Patient selection. Patient inclusion criteria for this study were as follows: Being within clinically operable stages, no clinically involvement of the nipple-areola complex, having information about exact tumor location, having at least 10 lymph nodes on dissection material, no prior specific treatment. Three hundred ninty-seven patients eligible were included in the study.

Statistical analyses. Statistical tests were performed using the SPSS 11.0 statistical software package for Windows (SPSS Inc, Chicago, IL). The differences in qualitative variables were evaluated by chi-squared test. Multivariate logistic regression analysis was created to assess different variables related to the NAC involvement. A receiver operating characteristic (ROC) analysis with the area under the ROC curve (AUC) was used for discriminating the best cut-off values, where necessary. All p-values were two side and a p-value of less than .05 was considered to indicate a statistically significant difference.

Table1. Clinical and pathologic characteristics of all patients and those with nipple-areola complex (NAC) involvement

Characteristic	n	(%)	NAC involvement, n	(%)
Age at diagnosis (years)				
<45	162	(41)	27	(17)
≥45	235	(59)	31	(13)
Tumor location				
peripheral	367	(92)	43	(12)
central	30	(8)	15	(50)
Pathologic T staging				
≤2 cm	87	(22)	9	(10)
>2 to 5 cm	243	(61)	27	(11)
>5 cm	67	(17)	22	(33)
Pathologic N staging				
Node negative	151	(38)	7	(5)
1 to 3 nodes	126	(32)	15	(12)
4 to 9 nodes	60	(15)	11	(18)
≥10 nodes	60	(15)	25	(42)
Pathologic stage				
1	75	(19)	6	(8)
2	235	(59)	27	(11)
3	87	(22)	25	(38)
Histologic grade				
1	21	(5)	2	(9)
2	170	(43)	27	(16)
3	179	(45)	28	(16)
unknown	27	(7)		
Lymphatic vascular invasion				
No	290	(73)	22	(8)
Yes	107	(27)	36	(34)
Estrogen receptor status				
positive	233	(59)	31	(13)
negative	128	(32)	22	(17)
unknown	36	(9)		
Progesterone receptor status				
positive	182	(46)	13	(7)
negative	94	(24)	17	(18)
unknown	121	(30)		
Total	397	(100)	58	(14.6)

Results

The median age was 47 (range 22 to 79) and median pathologic tumour size was 4.0 (range 0.5 to 7.0) cm. The median number of lymph nodes in dissection materials was 20 (range 10 to 47). Patients' characteristics were given in Table 1. Three hundred ten (78%) patients were in stage I and II, whereas 87 (22%) patients were in stage III. Sixty five patients (16%) of patients who had stage III disease had stage IIIC disease because of having more than 10 positive nodes and/or positive infraclavicular nodes.

The NAC involvement. The NAC involvement was confirmed histopathologically in 58 (14.6%) of the patients. The observed frequencies of the NAC involvement according to the different clinicopathologic variables were also shown in Table 1. The NAC involvement was more frequent in central tumors, in advanced pT and pN stages, and in presence of LVI than their counterparts. In the univariate analysis, these differences were statistically significant (Table 2).

The multivariate logistic regression analysis showed that tumor location, number of positive axillary lymph nodes, and LVI were the most important predictors of the NAC involvement (Table 3). According to this analysis, patients with central tumors, patients who had positive axillary lymph nodes equal to or more than 10, and those with LVI have a risk of the NAC involvement which are 7.5, 2.9, and 3.5 times higher than their counterparts, respectively. The best cut-off point of number of predictor factors for the risk of the NAC involvement was found as two by ROC analysis (AUC 0.79; 95%CI, 0.73-0.84).

Table 2. Predictors of NAC involvement in univariate analysis

Variable	p
Age (yrs) (≥45 vs <45)	NS
Tumor location (central vs peripheral)	0.0001
Tumor size (cm) (>5 vs ≤5)	0.0001
Histologic grade (2-3 vs 1)	NS
Number of positive lymph nodes (≥10 vs <10)	0.001
Lymphatic vascular invasion (Yes vs No)	0.0001
Estrogen receptor status (negative vs positive)	NS
Progesterone receptor status (negative vs positive)	NS

NS, not significant.

Table 3. Predictors of NAC involvement in multivariate analysis

Variable	HR	95% CI	p
Tumor location (central vs peripheral)	7.5	3.4-14,6	0.0001
Tumor size (cm) (>5 vs ≤5)			NS
Number of positive lymph nodes (≥10 vs <10)	2.9	1.3-6.1	0.005
Lymphatic vascular invasion (Yes vs No)	3.5	1.7-7.1	0.0001

HR, hazard ratio; CI, confidence interval.

Whereas 8 patients (3.8%) of 209 patients without any risk factor had the NAC involvement, the NAC involvement was observed in 19 (15.1%) of 126 patients with one risk factor, in 31 (50%) of 62 patients with two or three risk factors. Thus, high-risk group was accepted as patients with equal two or more than two risk factors and low-risk group was defined as those with no or one risk factor. The NAC involvement according to this risk groups was observed in 27 patients (8.1%) for the low-risk group and 31 patients (50%) for the high-risk group ($p<0.0001$).

Discussion

In the recent years, the trends in breast cancer surgery have been directed at balancing oncologically safe procedure with improved cosmesis. Thanks to developments of skin-sparing techniques with immediate reconstructions, even patients who want or need a mastectomy have anticipated a better aesthetic result. However, residual disease in the NAC caused local recurrence still continues to be a serious problem in patient selection for NAC-sparing surgery. Therefore, identification of patients at high risk for NAC involvement is still critical issue. Frequency of the occult NAC involvement in mastectomy specimens has been reported between 5.6 to 58% in the literature [3, 8–10]. Reasons of this wide range are not completely clear, but it may be due to different histopathological sampling methods used in different studies. In the presented study, the rate of occult NAC involvement in the mastectomy specimens was found as 14.6%. This rate indicates that even patients who had clinically normal NAC should be carefully selected for NAC-sparing mastectomy.

Various risk factors affected the NAC involvement have been reported in the literature. Some of these are clinical nipple involvement, skin involvement, tumor location, tumor to nipple distance, tumor size, axillary lymph node status, number of positive axillary lymph nodes, histologic grade, LVI, and tumor stage [5, 9, 10]. In this study, age, histologic grade, estrogen and progesterone receptor status had no significant effect on NAC involvement, whereas primary tumor size, tumor location, number of positive axillary lymph nodes, and LVI were the significant risk factors in the univariate analysis. The multivariate logistic regression analysis showed that central location, number of axillary lymph nodes, and LVI were independent predictors of NAC involvement.

One of the most analyzed prognostic factors of the NAC involvement in the literature is tumor size. Frequently, conventional mastectomy is performed to most of patients with tumor more than 5 cm. In a literature review, Patani et al. reported that SSM is an oncologically safe technique in patients with smaller than 5 cm invasive breast cancer [2]. Downes et al. [11] and Foster et al. [12] reported that only 2.6% and 4% developed a local recurrence after SSM, respectively, in the patients with advanced T and/or N stage that considered to be at high risk of local recurrence. In the presented study, although univariate analysis showed that T3 tumor significantly increased the risk of the NAC involvement, this factor had no effect on the NAC involvement in the multivariate analysis. Another risk factor investigated frequently in the studies is tumor location. Commonly accepted surgical treatment in centrally or subareolar located tumors is still mastectomy. A metaanalysis of mostly retrospective and partly prospective studies has shown that SSM with the NAC preservation was an oncologically safe treatment in selected patients [13]. However, in most of these studies, peripheral location of tumor has been accepted as the primary criterion for NAC preservation. In the presented study, the NAC was involved in 43 (12%) of 367 patients with tumor located in the peripheral zone, compared with 15 (50%) of 30 patients with tumor located in central area of the breast and this difference was statistically significant. On the other hand, the frequency of NAC involvement increased with increasing pN stage in this study, and we found that it was 5% in patients without positive axillary lymph nodes, 12% in patients with 1-3 positive axillary nodes, 18% in patients with 4-9 positive nodes. Additionally, the presence of ≥10 positive lymph nodes with a 42% rate of NAC involvement had the highest probability for NAC involvement. According to this result, it can be stated that the exact number of positive axillary lymph nodes is more accurate than axillary node status only to identify the risk of the NAC involvement. LVI is well known from the previous studies as a good predictor of locoregional recurrence [14] and axillary node involvement [15, 16]. However, there are a few studies about LVI as a predictor of NAC involvement. In two of these studies, it has been found that involvement of the NAC was associated with LVI [5, 10]. In the current study also, malignant infiltration rate of the NAC in patients with and without LVI was 34% and 8%, respectively, and this difference was statistically significant.

In the presented study, we constituted risk groups by using three risk factors including central location, number of axillary lymph node status, and LVI which were shown to have significant effects on NAC involvement in the multivariate analysis. The high-risk group was accepted as patients with equal two or more than two risk factors and the low-risk group was defined as those with no or one risk factor. The risk of NAC involvement was found 11.4 times higher in high-risk group compared to those low-risk group ($p<0.0001$). To our knowledge, the risk group stratification that constituted for the possibility of the NAC involvement is the first time in the literature.

In conclusion, our results revealed that the patients with centrally located tumor, ≥10 positive axillary lymph nodes, and LVI have a high-risk for the NAC involvement. Patients with two or three of these risk factors have the highest risk for malignant infiltration of the NAC. We concluded from this data that the NAC preservation might not offer a reasonable option for the patients in high-risk group because of inadequate local treatment and local recurrence risk. This procedure might be a suitable alternative intervention in the low-risk patients because of the observed rare malignant in-

filtration of the NAC. However, further studies are required to confirm the results of our study.

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