Correlating preoperative clinicopathological factors with skin and/or nipple–areola complex tumor involvement in postmastectomy specimens

Original Article

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ABSTRACT

Background: Breast cancer is the most commonly diagnosed cancer in women. Breast-conserving surgery is a common standard for treating many breast cancer patients. However, MRM (Modified radical mastectomy) is still done in ~ 30 % of patients undergoing surgeries. Our goal of the study is to identify factors that predict histopathological retro-areolar ducts and skin lymphatics tumor involvement, as well as to formulate bases extending the indication of skin sparing, especially nipple–areola complex (NAC) sparing mastectomy.

Patients and Methods: The study is an observational analytic study conducted on 145 cases. Inclusion criteria of the study are females sex, aged more than 18 years with locoregional breast disease who are candidates for MRM. Exclusion criteria are cases with grossly involved NAC, inflammatory breast cancer, skin ulceration, and nodules, Paget's disease of the nipple, and candidates for conservative breast surgery.

Preoperatively, all patients were subjected to a triple assessment of the breast cancer. Postoperatively, all mastectomy specimens are sent for the histopathological assessment.

Results: By univariate analysis, factors significantly affecting skin and NAC tumor involvement were age, tumor size, multifocality, nodal metastasis, histological grade, localized skin edema (peau d'orange), and lymphovascular invasion. By multivariate analysis, factors significantly increasing skin and NAC tumor involvement were nodal metastasis, localized skin edema, unexposure to neoadjuvant chemotherapy, and HER2 neo positive cases.

Conclusion: We can extend indications of SSM (Skin sparing mastectomy) in cases with negative nodal metastasis and absence of localized skin edema, who were exposed to neoadjuvant chemotherapy and HER2 neo negative cases.

Keywords: Nipple–areola complex tumor involvement, NAC sparing mastectomy, preoperative clinicopathological factors.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women nowadays and is the second after lung cancer as a cause of death in women[1]. In Egypt, the National Cancer Institute in Cairo registry reported breast cancer to be about 35.1 % of all diagnosed female cancers. Also, it was the most frequent cancer among El-Minia females in 2009, representing 26.8 % of all newly diagnosed female cancers[2].

Breast-conserving surgery is a common standard for managing many breast cancer patients nowadays, especially in early breast cancer, but mastectomy remains a necessary choice in about 30 % of patients undergoing surgeries, especially in cases with locally advanced breast cancer[3], also in cases with localized skin edema (peau d'orange) as it is thought to be due to occlusion of skin lymphatics by tumor emboli, so it represents a challenge for the preservation of either skin or nipple–areola complex (NAC)[4].

In skin-sparing mastectomy, we remove the nipple and the areola and conserve the rest of breast skin by because the nipple has terminal ducts that may harbor tumor cells or a certain amount of breast tissue posing a risk of subsequent cancer development[3].

Problems associated with reconstruction of the nipple after skin-sparing mastectomy include absence of projection, shape, size, color mismatch and position. Therefore, there is a growing interest in extending subcutaneous and NAC-sparing mastectomy in the hope of achieving better cosmetic and functional outcomes. NSM involves removing all breast tissue while preserving the entire skin of the breast and NAC[5].

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In many previous studies; age at diagnosis, tumor site, clinical T and N stage, tumor–nipple distance, response to hormonal therapy, localized skin edema (peau d'orange) and neoadjuvant chemotherapy play an important role in the choice of the procedure to be done[3].

Our aim in the current study is to identify clinicopathological criteria that predict histopathological retro-areolar ducts and skin lymphatics tumor involvement to formulate clinical and radiological bases extending the indication of skin sparing, especially NAC-sparing mastectomy.

PATIENTS AND METHODS

This research was performed at the Department of General Surgery, Faculty of Medicine, Helwan University, Helwan, Ethical Committee approval and written, informed consent were obtained from all participants.

This observational analytic study (including 145 patients) underwent mastectomy and was conducted at Helwan University Hospitals, Ain-Shams University Hospitals and Naser Institute (from June 2022 to June 2023).

Inclusions criteria of the study are female sex, aged more than 18 years with locoregional breast disease who are candidates for MRM, excluding patients with grossly involved NAC, inflammatory breast cancer, skin ulceration and nodules, Paget's disease of the nipple and candidates for conservative breast surgery.

Clinicopathological factors taken into consideration in the study include patient age, tumor size, pathological type, immunohistochemistry (estrogen receptor, progesterone receptor, HER2 NEU and KI67), distance between tumor and nipple, presence of localized skin edema (peau d'orange) in breast skin, exposure to neuadjuvant chemotherapy, multifocality, multicentricity and nodal metastasis. Postoperatively, all mastectomy specimens are inked and sectioned from medial to lateral into no greater than 1-cm-thick tissue sections and grossly examined. The nipples and areola are uniformly shaved, sectioned at 2–3 mm intervals vertically and submitted perpendicularly for microscopic examination. The identification of tumor cells in these sections is considered as NAC involvement. Tumor cells may present in the epidermis, dermis, hypodermis or terminal ducts opening into the nipple.

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0. (IBM Corp., Armonk, New York, USA). Qualitative data were described using number and percent. Quantitative data were described using mean and SD. The Kolmogorov–Smirnov test was used to verify the normality of distribution. The significance of the obtained results was judged at the 5 % level. The tests used were binary logistic regression, χ^2 test and Fisher's exact.

RESULTS

Table 1 shows the distribution of the studied cases according to clinicopathological factors in the study (n = 145).

Table 2 shows logistic regression analysis for the parameters affecting skin and NAC tumor involvement (n = 145).

Table 1: Distribution of the studied cases according to clinicopathological factors in the study (N = 145):

Patient age (μ, mean ± SD)	47.76 ± 11.93
Tumor type [n (%)]	
DCIS only	32 (22.1)
IDC	86 (59.3)
ILC	15 (10.3)
IDC + ILC	10 (6.9)
Others	2 (1.4)
Tumor stage [n (%)]	
T1	29 (32.6)
T2	35 (39.3)
T3	13 (14.6)
Nodal metastasis [n (%)]	
Negative	65 (44.8)
Positive	80 (55.2)
Histological grade [n (%)]	
Grade 1	44 (30.3)
Grade 2	77 (53.1)
Grade 3	24 (16.6)
Multifocality [n (%)]	
Absent	105 (72.4)
Present	40 (27.6)
Multicentricity [n (%)]	
Absent	125 (86.2)
Present	20 (13.8)
Single mass [n (%)]	
No (multifocality and/or multicentricity)	47 (32.4)
Yes	98 (67.6)
Localized skin edema (peaud'orange) [n (%)]	
Negative	112 (77.2)
Positive	33 (22.8)
Lymphovascular invasion [n (%)]	
Negative	91 (62.8)
Positive	54 (37.2)
Tumor to nipple distance [n (%)]	
≤ 2 cm	85 (58.6)

> 2 cm	60 (41.4)
Estrogen receptor [n (%)]	
Negative	23 (15.9)
Positive	122 (84.1)
Progesterone receptor [n (%)]	
Negative	39 (26.9)
Positive	106 (73.1)
Her2/neu [n (%)]	
Negative	101 (67.4)
Positive	43 (32.6)
Equivocal	1 (0.7)
Ki67 [n (%)]	
Low	102 (70.3)
High	43 (29.7)
Neoadjuvant chemotherapy [n (%)]	
Negative	94 (64.8)
Positive	51 (35.1)
Skin and/or NAC tumor involvement [n (%)]	
Negative	115 (79.3)
Positive	30 (20.7)

Table 2: Logistic regression analysis for the parameters affecting skin and nipple–areola complex tumor involvement (N=145):

			Univariate analysis			Multivariate analysis		
			CI			CI		
Positive skin and/or NAC tumor involvement [n (%)]			**Lower**	**Upper**	***P* value**	**OR**	**Lower**	**Upper**
Age at diagnosis		0.008	1.048	1.012	1.085	0.966	1.001	0.949	1.056
Tumor type								
DCIS	0	0.9	0.00	0.000				
IDC	19 (22.1)	0.62	1.24	0.540	2.838			
ILC	5 (33.3)	0.21	2.1	0.659	6.690			
IDC + ILC	6 (60)	0.005	6.94	1.817	26.491			
Others	0	0.999	0.00	0.000				
Tumor size		0.000	2.194	1.526	3.153	0.224	1.443	0.799	2.605
Nodal metastasis								
Negative	2 (3.1)							
Positive	28 (35)	0.000	16.962	3.858	74.571	0.004	16.600	2.447	
Histology grade								
Grade 1	0	0.997	0.000	0.000				
Grade 2	18 (23.4)	0.397	1.424	0.629	3.222			
Grade 3	12 (50)	0.000	5.722	2.227	14.706	0.082	6.175	0.793	48.056
Multifocality (+ve)	15 (37.5)	0.003	3.600	1.551	8.353	0.593	1.640	0.268	10.040
Multicentricity (+ve)	8 (40)	0.027	3.121	1.141	8.536	0.849	0.843	0.146	4.878
Single mass	12 (12.2)							
Localized skin edema (Peau d'orange)								
Negative	11 (9.8)							
Positive	19 (57.6)	0.000	12.461	4.919	31.564	0.023	10.297	1.370	77.385
Lymphovascular invasion								
Negative	10 (11)							

Positive	20 (37)	0.000	4.765	2.020	11.240	0.051	6.061	0.993	36.985
Tumor to nipple distance									
≤ 2 cm	21 (24.7)	0.159	0.538	0.227	1.275	0.224	0.389	0.085	1.781
> 2 cm	9 (15)								
ER									
Negative	6 (26.1)								
Positive	24 (19.7)	0.488	0.694	0.247	1.948	0.074	0.091	0.007	1.264
PR									
Negative	9 (23.1)								
Positive	21 (19.8)	0.667	0.824	0.340	1.995	0.133	4.960	0.614	40.064
Her2 neu									
Negative	16 (15.8)								
Positive	14 (32.6)	0.048	2.225	1.007	4.916	0.019	5.256	1.311	21.071
Equivocal	0								
Ki67									
Low	17 (16.7)								
High	13 (30)	0.069	2.167	0.941	4.986	0.406	0.519	0.110	2.443
Neoadjuvant chemotherapy									
Negative	22 (23)								
Positive	8 (15.7)	0.276	0.609	0.249	1.487	0.007	0.065	0.009	0.466
Constant (multivariate)		0.028	0.008						

CI, confidence interval; LL, lower limit; NAC, nipple–areola complex; OR, odd's ratio; UL, upper limit.
P: *P* value for odd's ratio for comparing between the studied groups.
*Statistically significant at P value less than or equal to 0.05.

All factors were correlated to positive skin and/or NAC tumor involvement and the following results were obtained:

The OR of positive nodal metastasis, presence of peau d'orange and positive Her 2 neo cases is more than one, which means negative association between them. The OR of patients who were exposed to neoadjuvant chemotherapy is less than 1, which means negative association between them.

DISCUSSION

Over the past 60 years, there have been many studies on the factors associated with skin and/or NAC involvement in breast cancer and there is a notable advancement in the surgical treatment of breast cancer. This can be seen in the widespread acceptance of skin-sparing mastectomy, which preserves the original skin cover, offering great improvements in early and delayed breast reconstruction surgery[6].

This study was conducted on 145 patients with a mean age at diagnosis of 47.76 years. In 20.7 % of instances, skin and/or NAC tumor involvement was positive; in 79.3 % of cases, it was negative. This is within the range that Gomez *et al.*[7] found that the incidence of nipple involvement might be anything between 0 and 58 %. A larger percentage based on research by Pirozzi *et al.*[8], with 50 individuals involved in the study, 12 (24 %) having NAC involved and 38 (76 %) not. Thirty-one of the 272 conventional mastectomies and 31 nipple-sparing mastectomies performed in the Huang *et al*. [9] trial, 13.2 % of them had NAC involvement.

In contrast, the study by Pirozzi and colleagues found that the average age was 58.1 (13.2) years, ranging from 27 to 87 years. Patients in group B had a mean age of 55.8 (12.5) years, while patients in group A, where the NAC had no effect, had a mean age of 58.9 (13.5) years (P = 0.477). When age was split into two groups, those under 50 and those over 50, a statistically significant difference was seen between them[8].

On the contrary, Goda and colleagues discovered that the mean age of patients with breast cancer who did not have NAC invasion was not significantly higher than the mean age of those who did (mean: 51.26 vs. 49.90 years, P = 0.741). Additionally, no significant correlation was found between the age group and NAC invasion, with 26 % of patients without NAC invasion being younger than 40 years old and 18.2 % of patients with NAC invasion. Also, it is found that smaller tumors (6 – 10 % for in-situ tumors and 7 – 8 % for

invasive tumors, respectively) had a lower likelihood of nipple involvement (18 %, $P = 0.0032$) and invasive carcinomas (20 %, $P = 0.0014$) compared to tumors larger than 5 cm[10].

According to the previously mentioned data, there was a strong correlation between older patients, larger tumor size and positive skin and/or NAC tumor involvement.

According to Goda and colleagues, there is a substantial correlation between clinical N stage and NAC invasion, with N3 being present in 20 % of patients without NAC invasion compared to 63.6 % of patients with NAC invasion ($P = 0.014$), which is consistent with our results. Histological grade and NAC invasion are significantly correlated; grade III was seen in 40 % of patients without NAC invasion and 90.9 % of patients with NAC invasion ($P = 0.002$). Node positivity was seen in 60 % of patients without NAC invasion and 100 % of individuals with NAC invasion ($P = 0.011$). Patients with NAC invasion had a substantially larger number of positive lymph nodes than patients without NAC invasion (mean: 13.72 vs. 4.98, $P = 0.001$)[10].

Information from Lambert *et al.*[11] showed that a higher tumor's nuclear grade was associated with a 10-fold increased risk. There was a substantial correlation between tumor grade and nodal metastasis and skin and/or NAC tumor involvement in concordance with our study. The findings of Faisal *et al.*[12] corroborate our findings since they discovered lymphovascular invasion in 41.7 % of patients with NAC involvement as opposed to 12.8 % of individuals without NAC involvement.

On the other hand, Pirozzi *et al.*[8] discovered that out of 50 cases, 15 had lymphovascular invasion, 14 of which were in the group whose nipples were unaffected and just one in the group whose nipples were involved. The comparison between the two groups did not reveal any statistically significant differences. These results contradict those of Vyas *et al.* (1998) and Vlajcic *et al.* (2005)[14], presumably a result[13] of due to the Pirozzi and colleagues study's smaller sample size. It is important to remember that surgical pathology relies on sampling procedures and that all tumors involving lymph nodes inherently include lymphovascular invasion. Therefore, despite contradictory scientific studies, we believe these parameters cannot be regarded as determinants of NAC participation.

In line with our findings, there was a strong correlation between skin and/or NAC tumor involvement and lymphovascular invasion and cutaneous edema (peau d'orange). Pirozzi *et al.*[8] discovered no significant changes in progesterone receptor and estrogen receptor status between the groups mentioned in this study ($P = 0.794$ and 0.825, respectively), which is consistent with our results.

Goda and colleagues, on the other hand, discovered a significant correlation between NAC invasion and estrogen receptor negativity, with 18 % of patients without NAC invasion having negative estrogen receptors versus 90.9 % of patients with NAC invasion ($P < 0.001$). Additionally, there is a significant correlation between progesterone receptor negativity and NAC invasion, with 24 % of patients without NAC invasion having negative progesterone receptor versus 72.7 % of patients with NAC invasion ($P = 0.004$) and HER2 positivity and NAC invasion with 8 % of patients without NAC invasion having positive HER2/neu versus 90.9 % of patients with NAC invasion ($P < 0.001$)[12]. There was no relation between skin and/or NAC tumor involvement and hormonal receptor status.

CONCLUSION

By univariate analysis, factors significantly affecting the skin and NAC tumor involvement were age, tumor size, multifocality, nodal metastasis, histological grade, localized skin edema (peau d'orange) and lymphovascular invasion.

By multivariate analysis, factors significantly increasing skin and NAC tumor involvement were nodal metastasis, localized skin edema, unexposure to neoadjuvant chemotherapy and HER2 neo positive cases. We can extend indications of SSM in cases with negative nodal metastasis and absence of localized skin edema, who were exposed to neoadjuvant chemotherapy and HER2 neo negative cases.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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