Predictors of occult nipple–areola complex involvement in breast cancer patients: clinicopathologic study

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Context
Although oncoplastic breast-conserving surgery is a standard approach for treatment of breast cancer patients, mastectomy is still performed in 20–30% of patients undergoing surgeries. Nipple-sparing mastectomy provides a cosmetic and psychological outcome for patients; however, the oncologic safety of nipple–areola complex (NAC) sparing is a major concern.
Aim
The focus of this study was to determine the predictive factors of NAC involvement to define the indicators for NAC preservation.
Patients and methods
We analyzed NAC involvement in 180 patients during the period between October 2013 and December 2016 as regards the relation between the pathological affection of the NAC and clinical criteria, pathological and molecular features of the tumor (size, site, tumor–nipple distant, nodal affection, and molecular classification of breast cancer).
Results
Among 180 patients, 38 (21.1%) demonstrated NAC involvement, and it was mostly associated with tumor size 4 cm (P=0.047), tumor–nipple distant of 2.5 cm (P=0.003), positive lymph node (P=0.05), negative estrogen receptor (P=0.00013), negative progesterone receptors (P=0.000001), and HER2 receptor overexpression (P=0.001). Triple-negative breast cancer was significantly associated with increased risk of NAC involvement followed by HER2/neu-enriched subtype (P=0.001).
Conclusion
Tumor–nipple distant, tumor size and state of lymph nodes are the most important clinical predictors of nipple involvement and should be considered as risk factors. At the pathological and molecular level, triple-negative breast cancer is the worst subtype. The presence of one or more of these factors indicates high risk of occult nipple invasion.

Keywords:
nipple involvement, nipple-sparing mastectomy, predictive factors

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Introduction

Although oncoplastic breast-conserving surgery is a standard approach for treatment of breast cancer patients, mastectomy is still performed in 20–30% of patients undergoing surgeries [1,2].

Skin-sparing mastectomy and nipple-sparing mastectomy (NSM) are examples of mastectomy techniques that were originally employed for benign lesions [3,4].

Skin-sparing mastectomy requires the removal of the nipple–areola complex (NAC) by considering the fact that the nipple contains the terminal ducts that may contain tumor cells or a certain amount of breast tissue that carry a risk of developing subsequent cancer [5].

There are many problems with reconstructed nipples, including lack of projection, shape, size, color mismatch, and position. Hence, there is increasing interest in preservation of the NAC in the hope of achieving better cosmetic and functional outcomes [6–9].

NSM includes removal of all breast tissue with preservation of the entire skin of the breast and NAC [10,11].

Risk factors for NAC involvement with tumor are still not well defined. Therefore, selection criteria for NSM in breast cancer patients have not been well established [12].

We intended to investigate the frequency of occult NAC involvement and the clinicopathologic factors most frequently associated with it.

Aim

The focus of this study was to determine the predictive factors of NAC involvement to define the indicators for NAC preservation.

Patients and methods

This study was conducted at Zagazig University Hospital between October 2013 and December 2016. The study was approved by local ethical committee of our faculty and the technique was discussed with all patients and informed consent was obtained. In this study, we analyzed NAC involvement in 180 patients as regards the relation between the pathological affection of the NAC and clinical criteria of the tumor [size, site, tumor–nipple distant (TND), and nodal affection].

Inclusion criteria

All female patients with breast cancer with healthy non invaded skin and grossly free NAC and who were not candidates for oncoplastic surgery.

Exclusion criteria

(1) Grossly and radiologically involved NAC.
(2) Inflammatory breast cancer.
(3) Breast cancer patient subjected to chemotherapy or radiotherapy.
(4) Skin involvement.

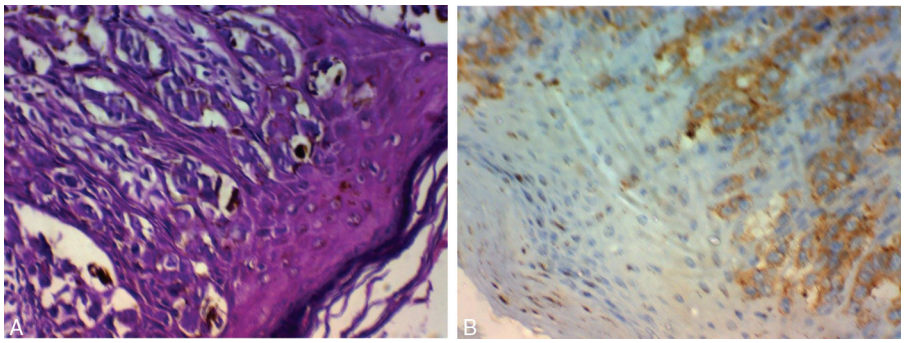
All patients diagnosed with breast cancer by history taking, clinical examination and investigation in the form of breast ultrasound, mammography and biopsy [Fine needle aspiration cytology (FNAC), true cut or excisional]. For staging of the disease chest radiography, pelvic abdominal ultrasound and bone scan were carried out. MRI was performed for all patients to measure TND (distant between the center of the nipple and nearest margin of the lesion).

After diagnosis of early breast cancer, our patients were prepared and consented for modified radical mastectomy (MRM).

Clinical criteria of the patients that were taken into consideration throughout our study included age, tumor size, tumor site, lymph node status (palpable or not palpable) and TND. Breast ultrasonography plays an important and more precise role in determining tumor size and infiltration of axillary lymph nodes.

The resulting specimens after MRM were subjected to histopathological examination for nipple invasion (lymphatic and vascular invasion of the subareolar region) (Fig. 1) shows histological type [Invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), ductal carcinoma insitu (DCIS) or any combination], tumor grade (I, II or III), pathological lymph node affection (positive or negative) and immunohistochemistry for molecular classification: (i) luminal A tumors that showed an IHC profile of high Estrogen receptors (ER), progesterone receptors (PR) expression, negative HER2 and low Ki67; (ii) luminal B is ER+, PR+, HER2– and Ki67 greater than or equal to 14%; (iii) luminal HER2 is ER+, PR+ and HER2+; (iv) HER2-enriched subtypes are ER–, PR–, HER2+ and (v) triple-negative breast cancer (TNBC): ER-, PR- and HER2-. Immunohistochemistry was performed on paraffin sections using anti-ER antibody (clone D07, DAKO) and anti-PR antibody ((PR 636, Dako at 1 : 50 dilution). Polyclonal HER2 antibody in the Herceptin kit (HercepTest, DAKO) was used according to the manufacturer's instructions and

Figure 1



A: Skin of NAC are infiltrated by malignant ductal epithelial cells (H&E x400). B: Skin of NAC are infiltrated by malignant ductal epithelial cells (IHC, Her2-neu x400).

Ki67 antibody (clone MIB-1, 1 : 50 dilution; Dako) was utilized by using the Envision system for detection. For ER and PR expression, moderate to strong nuclear staining in ≥1% of tumor cells was considered positive. HER2/neu was considered positive if at least 10% of tumor cells exhibited 3+ cell membrane staining. Cutoff point for ki67 expression was 14%.

Statistical analysis was performed to compare tumors with or without nipple involvement.

Results

Patient age

Age distribution along the examined group is shown in Table 1

Lymph nodes examination

In our study, preoperative examination of axillary lymph nodes revealed that the majority of cases had impalpable nodes, but on testing the relation of having infiltrated axillary LNs to having an NAC devoid of malignancy, this relation was found to be strongly statistically significant as *P* value was less than 0.05 (χ^2 test was used) (Table 2).

Tumor–nipple distant

In our study, preoperative measuring of the distant from the outer mass margin to the center of the nipple was recorded in a trial to find the safe distance at which the NAC was devoid of malignancy. Patients were divided into groups as shown in the following table; thereafter, every 2 successive groups were compared statistically to record this safe distance, and at least 2.5 cm was found to be the statistically significant safe distant for having an NAC free of malignancy. *P* value was 0.003 (χ^2 test was used) (Table 3).

Table 1 Age distribution along the examined group

Age	NAC positive	NAC negative	Total	χ^2	*P* value
<30	0	4	4	1.129	0.769
30–<40	8	31	39		
40–60	21	75	96		
>60	9	32	41		
Total	38	142	180		

NAC, nipple–areola complex.

Tumor size

In our study, tumor size at the maximal diameter was recorded in a trial to find the safe size at which the NAC was devoid of malignancy. Patients were divided into groups as shown in the following table; thereafter every 2 successive groups were compared statistically to record this safe size and 4 cm at maximal diameter for the tumor mass was found to be the statistically significant safe size for having an NAC free of malignancy. *P* value was 0.047 (χ^2 test was used) (Table 4).

Other pathological features

In our study, certain pathological factors were recorded in a trial to outline the pathological features at which the NAC was devoid of malignancy. These factors were as follows:

(1) Histopathological type of the tumor.
(2) Histological grade.
(3) Histopathological status of lymph nodes.
(4) Molecular classification of breast cancer.

It was found that histopathological type of the tumor, histological grade or histopathological status of lymph nodes cannot affect the malignancy-free condition of the NAC, as *P* values for them were 0.687, 0.084, and 0.08,

Table 2 State of lymph nodes

Clinical examination of lymph nodes	NAC positive	NAC negative	Total	χ^2	*P* value
Clinically positive	29	36	65	33.748	<0.05 (too low)
Clinically negative	9	106	115		
Total	38	142	180		

NAC, nipple–areola complex.

Table 3 Tumor–nipple distant

Tumor–nipple distant (cm)	NAC positive	NAC negative	Total	χ^2	*P* value
<2	19	20	39	41.2	0.0001
2–<2.5	18	28	46		
2.5–<3	1	20	21		
3–<3.5	0	41	41		
3.5–<4	1	20	21		
>4	0	12	12		
Total	38	142	180		

NAC, nipple–areola complex.

Table 4 Tumor size

Tumor size (cm)	NAC positive	NAC negative	Total	χ^2	*P* value
<1	0	13	13	25.1	0.00004
1–<2	2	15	17		
2–<4	9	66	75		
4–<5	12	34	46		
>5	15	14	29		
Total	38	142	180		

NAC, nipple–areola complex.

Table 5 Pathological finding

Pathological findings	NAC positive	NAC negative	Total	χ^2	*P* value
Histopathological type					
IDC	34	120	154	0.749	0.687
ILC	1	8	9		
IDC+DCIS	3	14	17		
Total	38	142	180		
Histological grade					
Grade I	1	17	18	4.94	0.084
Grade II	19	80	99		
Grade III	18	45	63		
Total	38	142	180		
Pathological lymph nodes					
Positive	24	67	91	3.06	0.080
Negative	14	75	89		
Total	38	142	180		
Estrogen receptors					
Positive	16	106	122	14.537	0.00013
Negative	22	36	58		
Total	38	142	180		
Progesterone receptors					
Positive	11	102	113	23.593	0.000001
Negative	27	40	67		
Total	38	142	180		
HER2 overexpression					
Positive	23	46	69	10.036	0.001
Negative	15	96	111		
Total	38	142	180		

NAC, nipple–areola complex.

Table 6 Molecular classification of the cases

	NAC positive	NAC negative	Total	*P* value
Luminal A	4	66	70 (38.9)	0.001
Luminal B	4	36	40 (22.2)	
Luminal HER2	3	27	30 (16.7)	
HER2 enriched	11	11	22 (12.2)	
TNBC	16	2	18 (10)	
Total	38 (21.1)	142 (78.9)	180	(100)

NAC, nipple–areola complex; TNBC, triple-negative breast cancer.

respectively. In contrast, estrogen and progesterone receptors status and HER2 overexpression were found to strongly and significantly affect the malignancy-free condition of the NAC, as *P* values for them were 0.00013, 0.000001 and 0.001, respectively (χ^2 test was used), as shown in Table 5. TNBC was significantly associated with increased risk of NAC involvement followed by HER2/neu-enriched subtype (*P*=0.001) as shown in Table 6.

Discussion

Surgical treatment of early breast cancer has rapidly evolved from radical mastectomy to more cosmetic

procedures like breast-conserving surgery and NSM with NAC preservation.

All patients in our study were subjected to MRM, because we included patients who were not candidates for oncoplastic surgery (patient preference was the main cause) and to enable us for NAC resection and histopathological examination.

Most breast cancer patients ask for both better cosmetic appearance and oncological safety. The majority of patients are interested in preserving the nipple during surgical resection of the tumor.

Preoperative detection of NAC invasion helps the surgeon to choose the most suitable surgical procedure that achieves both cosmetic and oncological satisfaction.

Factors that predict NAC invasion are not fixed in all studies, and to preserve the NAC we must be sure that it is free from malignancy.

The rate of NAC involvement has shown a wide range of involvement varying from 0 to 58% [13,14]; hence, the safety of the NSM remains controversial. NAC involvement was defined by the presence of invasive carcinoma and/or ductal carcinoma *in situ* at the subareolar margin. In this work we tried to predict factors that determine NAC involvement. In the current study NAC involvement was 21.1%; however, Andersen and Pallesen [15] have reported a rate of 50% of NAC involvement.

Many studies reported a lower rate of recurrence; Laronga *et al*. [16], have reported a 5.6% rate of recurrence, whereas Jianli *et al*. [17] reported a 9.5% rate of recurrence. This discrepancy between different rates of recurrence may be due to a peripherally located tumor in some studies and the sampling technique of the nipple, whether it was a sagittal section, or multiple coronal or vertical sections.

Site of the tumor, size of the tumor, and the state of the lymph nodes are the most important clinical factors associated with NAC involvement [18,19]; this was confirmed in the current study.

In our study, TND was the most important risk factor for nipple invasion; tumor distance less than 2.5 cm from the nipple was predictive for NAC involvement, and this is in agreement with Gerber *et al*. [9] and Vyas *et al*. [20], but in contrast with Sacchini *et al*. [7] who report that the cutoff value of TND was 1 cm.In this study, the risk of NAC invasion is directly proportionate with tumor size; tumor size less than 4 cm in our study was predictive for NAC involvement, and this is in agreement with Garcia-Etienne *et al*. [21].

In our study, breast ultrasonography plays an important and more precise role in determining axillary lymph nodes infiltration; positive lymph nodes were predictive for NAC involvement.

Breast cancer is a heterogeneous tumor that reveals several different molecular profiles with different biological behaviors; triple-negative subtypes present poorly differentiated tumors lacking ER, PR, and HER2 on immunohistochemical assay, and they are characterized by an increased rate of proliferation and increased invasiveness. In this work, this subtype was associated with increased risk of NAC involvement followed by HER2/neu-enriched subtype and this is in agreement with Petit *et al*. [22].

Conclusion

Tumor nipple distant, tumor size and state of lymph nodes are the most important clinical predictors of nipple involvement and should be considered as risk factors. At the pathological and molecular level, TNBC is the worst subtype. The presence of one or more of these factors indicates high risk of occult nipple invasion.

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Conflicts of interest

There are no conflicts of interest.

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