Prediction of nipple and areola complex invasion in breast cancer patients: clinical and pathological study of surgical specimens

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Background
Nipple–areola sparing (NAS) mastectomy is nowadays considered the most common conservative procedure used for both risk reduction (prophylaxis) and cancer treatment. We regard the oncological safety as a first concern in the management of breast cancer (BC) patients.
Aim
The aim of this study was to assess the predictive value of clinical and pathological criteria that might affect decision making for NAS mastectomy in BC patients.
Patients and methods
This study included 60 cases of operable BC that underwent MRM. All specimens were subjected to histopathological examination of the subareolar tissue to prove or disprove malignant infiltration of the nipple–areola complex (NAC), and their data were plotted against the preoperative predictive factors.
Results
The incidence of occult NAC malignancy was 15%. Predictive factors influencing NAC invasion were tumour–nipple distance less than 4 cm, grade III tumour, lymph node metastasis, lymphovascular invasion, human epidermal growth factor receptor-2 positivity, oestrogen receptor/progesterone receptor negativity, retroareolar/centrally located tumour and multicentric tumours.
Conclusion
NAS mastectomy for the management of BC would be appropriate in carefully selected patients who have peripherally located tumours, grade I or II, not multicentric or multifocal, with tumour-to-nipple distance greater than 4 cm, and human epidermal growth factor receptor-2 negative with no lymphovascular invasion of the subareolar plexus or axillary lymph nodes metastasis.

Keywords:
breast cancer, nipple–areola complex, nipple–areola sparing mastectomy

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Introduction

Breast cancer (BC) remains the most frequently diagnosed cancer among women. Surgical techniques have evolved from radical mastectomy to less invasive and cosmetically acceptable surgical approach in recent years [1].

Mastectomy is a common surgical option in case of BC treatment or prophylaxis. It is considered as an operation that is associated with several problems for the patient, affecting the overall postoperative quality of life: altered body image, diminished self-worth and loss of a sense of feminity along with anxiety and depression [2].

Oncoplastic breast surgery is becoming popular, aiming to provide adequate oncological clearance of a tumour with attention to breast aesthetics [3].

Nipple–areola sparing (NAS) mastectomy is nowadays considered the most conservative procedure that improves the overall quality of life for women, allowing excellent cosmetic results because it provides a natural-appearing breast [4].

The NAS mastectomy reconstruction is related to autologous and alloplastic techniques and sometimes includes contralateral breast surgery [5].

In addition to the aesthetic benefits of NAS mastectomy, recent studies reported low rates of local recurrence and no significant difference

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between long-term follow-up between NAS mastectomy and mastectomy [6].

Many factors affect nipple involvement (NI) and areola involvement, such as patient's age, tumour size, tumour location (central vs. peripheral), tumour-to-nipple distance, lymphovascular invasion (LVI), lymph node metastasis, histological type and grade of the tumour and multifocal/multicentric tumour [7].

We designed this study to evaluate factors that affect nipple–areola complex (NAC) invasion to put the selection criteria for NAS mastectomy.

Patients and methods

This study was carried out in the Department of General Surgery and Department of Pathology, Faculty of Medicine, Zagazig University Hospitals, during the period from January 2014 to July 2016. The study was complied with the local guidelines of the research IRB/ ethics committee of Zagazig University Hospitals and all patients included gave informed consents. The study included 60 Egyptian female patients with BC; all of them were subjected to modified radical mastectomy (MRM) operation.

Inclusion criteria were as follows:

(1) Female patient more than 18 years.
(2) BC patients with healthy looking noninvaded skin of the nipple and areola.

Exclusion criteria were as follows:

(1) Age less than 18 years.
(2) Refusal to participate.
(3) Being unfit for surgery.
(4) Previously subjected to chemotherapy or radiotherapy for BC.
(5) Inflammatory BC cases.
(6) Presence of skin changes involving NAC.

In this study, we evaluated the oncological safety for NAS mastectomy procedure by searching for the factors that predict the presence of NAC invasion. This procedure is performed by history taking and clinical examination. Thereafter, we searched for the presence of the occult malignant cells in the subareolar tissue in the breast specimens of the standard MRM.

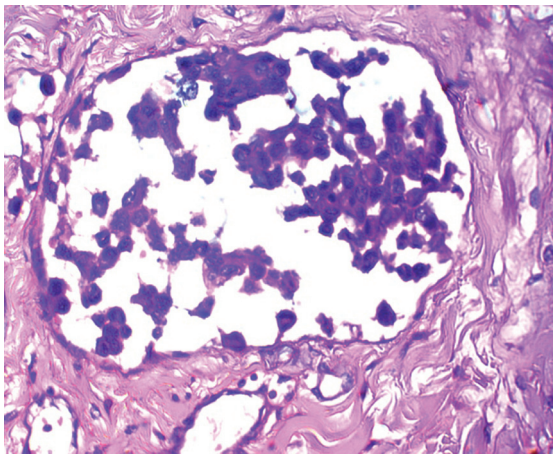
Standard MRM was performed for all patients, removing all breast tissue, the NAC, necessary skin and total axillary lymph nodes.

Breast specimen was examined by a single expert pathologist using standard hematoxylin and eosin stains under light microscopy. Tissue just underlying the NAC was examined for evidence of malignancy (Fig. 1).

All specimens were examined by a single expert pathologist to search for malignancy in the subareolar tissue.

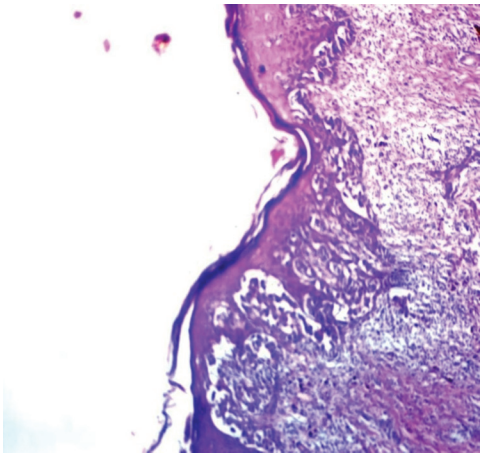
Immunohistochemistry was performed on paraffin sections by using anti-ER antibody (Clone D07, 1 : 50 dilution; Dako, Denmark), anti-PR antibody (PR 636, 1 : 50 dilution; Dako, Denmark) and polyclonal human epidermal growth factor receptor-2 (HER2) antibody in the Herceptin kit (Hercep test; Dako, Denmark), according to the manufacturer's instructions by using EnVision System (Dako, Denmark) for detection. For oestrogen receptor

Figure 1



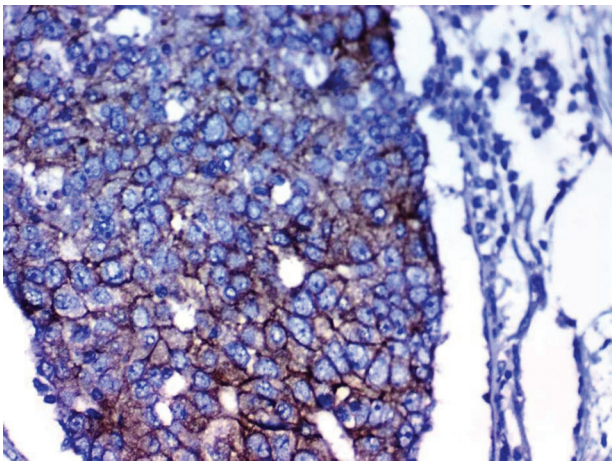
Infiltrating duct carcinoma (IDC) grade III showing malignant ductal epithelial cells inside the vessel lumen (tumor emboli) (H&E ×400).

Figure 2



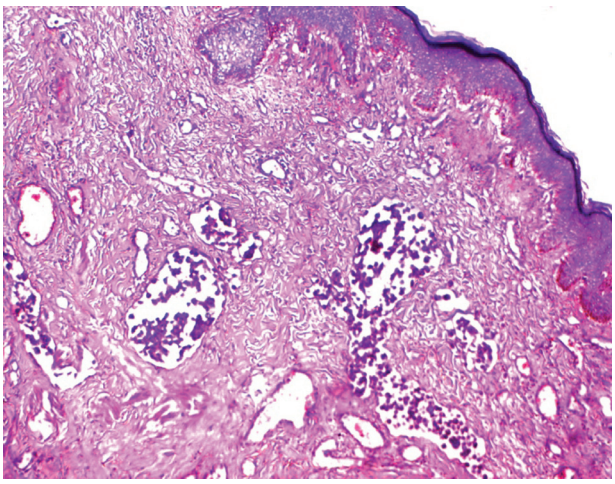
Infiltrating duct carcinoma (IDC) grade III, showing infiltration of the overlying epidermis by groups of malignant ductal epithelial cells (H&E ×100).

Figure 3



Infiltrating duct carcinoma (IDC) grade III, showing positive HER2 /neu membranous immunoreactivity (Score 3) (IHC ×400).

Figure 4



Infiltrating duct carcinoma (IDC) grade III, showing lymphovascular invasion in the subareolar plexuses (tumor emboli) (H&E ×100).

(ER) and progesterone receptor (PR) expression, moderate-to-strong nuclear staining in 1% or more of tumour cells was considered positive. HER2/neu was considered positive if at least 10% of tumour cells exhibited 3+ membranous staining (Fig. 2–8).

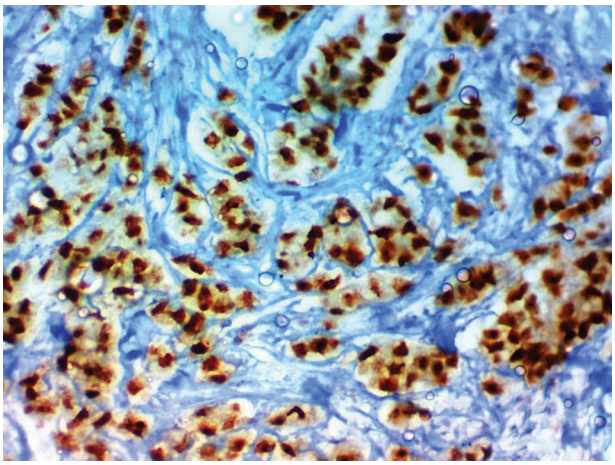
Statistical analysis

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean±SD for quantitative variables. For categorical variables Fisher's exact test or χ^2-test was used. A *P* value less than 0.05 was considered significant.

Results

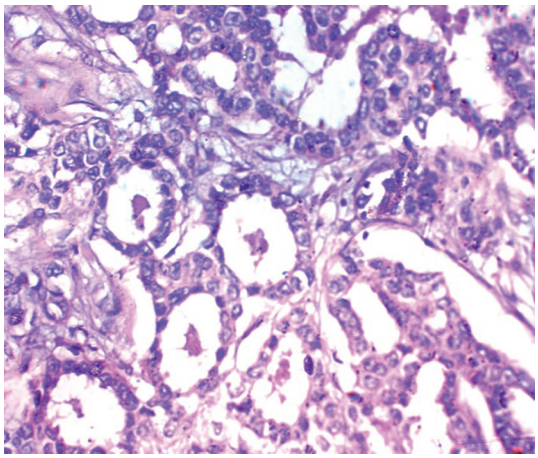
A total of 60 patients were included in this study. Their ages ranged from 28 to 78 years with a mean age of 51.1 years (Table 1).

Figure 5



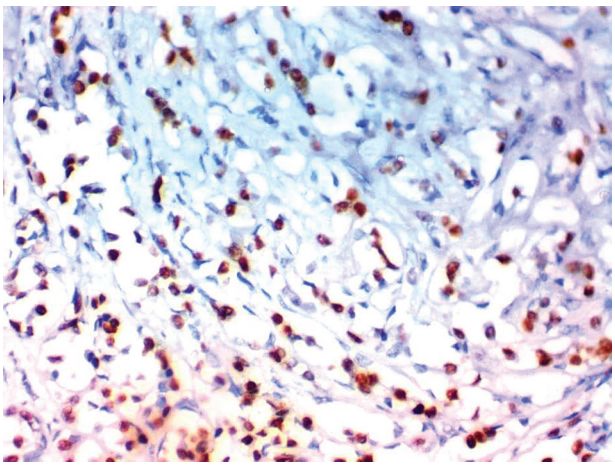
Infiltrating duct carcinoma (IDC) grade III, showing strong PR nuclear immunoreactivity (IHC ×400).

Figure 6



Infiltrating duct carcinoma (IDC) grade II, showing tubular formation (H&E ×400).

Figure 7



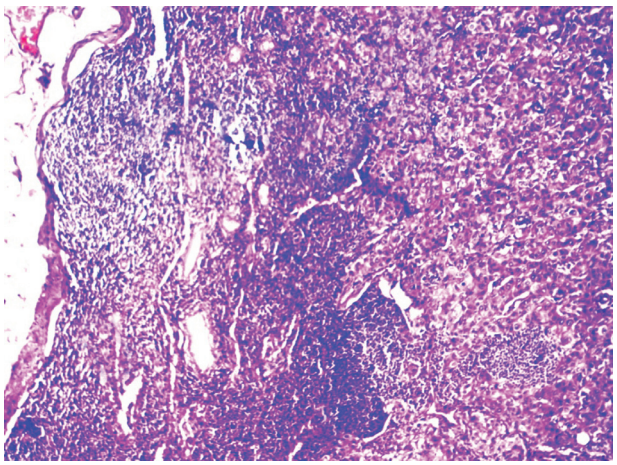
Infiltrating duct carcinoma (IDC) grade III, showing strong ER nuclear immunoreactivity (IHC ×400).

We included 60 patients: one of them had bilateral BC and nine of them had multifocal BCs; each one had two masses. Therefore, we had 60 patients, 61 breasts and 70 masses.

There was no statistically significant association between the age and menstrual state of the patient and NAC invasion (P=0.121 and 0.558, respectively). Moreover, there was no statistically significant association between positive family history of BC and NAC invasion (P=1.000) (Table 1).

However, there was a statistically significant association between nipple retraction as a patient's complaint and NAC invasion, in which 2% of patients were without NAC invasion complaint of nipple retraction versus 36.7% of patients with NAC invasion (P=0.001) (Table 2).

Figure 8



Lymph node positive for IDC, showing loss of normal nodal architecture that's replaced by malignant ductal epithelial cells (H&E ×100).

There was no statistically significant association between breast size and NAC invasion (P=0.186) (Table 2). However, there was a highly statistically significant association between centrally located tumours and NAC invasion (P<0.001) (Table 2).

Multifocal tumours were associated with statistically significantly higher incidence of NAC invasion (P<0.001) (Table 3). However, there was no statistically significant association between tumour size neither clinically assisted or ultrasound-assisted and NAC invasion (P=0.401 and 0.838, respectively) (Table 4).

There was a highly statistically significant association between the mass-to-nipple distance and NAC invasion (P<0.001) (Table 5).

There was a statistically significant association between the histological grade of the tumour and NAC invasion (P=0.002) (Table 6).

Number of positive lymph nodes in patients with NAC invasion was significantly higher than the number of patients without NAC invasion (P=0.011) (Table 6).

There were statistically significant associations between ER negativity, PR negativity, and HER2 positivity and NAC invasion (P<0.001, 0.004, 0.001, respectively) (Table 7).

Discussion

Oncoplastic surgery has become a key aspect of BC treatment, as it considers both oncological and cosmetic outcomes. The idea of sparing the skin of the breast is to facilitate the immediate breast reconstruction [8].

Table 1 Demographic data of the studied groups

Demographic data	NAC invasion [*n* (%)]		Tests	*P* value (significance)
	Absent (*N*=50)	Present (*N*=11)		
Age (years)				
Mean±SD	51.26±12.56	49.90±10.26	0.332[a]	0.741 (NS)
Median (range)	52 (28–76)	49 (33–62)		
<40	13 (26)	2 (18.2)	4.224[b]	0.121 (NS)
40–60	20 (40)	8 (72.7)		
>60	17 (34)	1 (9.1)		
Menstrual state				
Premenopausal	18 (36)	5 (45.5)	0.343[b]	0.558 (NS)
Postmenopausal	32 (64)	6 (54.5)		
Family history				
Negative	37 (74)	8 (72.7)	0.008[b]	1.000 (NS)
Positive	13 (26)	3 (27.3)		

NAC, nipple–areola complex. [a]Independent samples Student's *t*-test. [b]χ^2-test. P<0.05, significant.

Table 2 Clinical data of the studied groups

Clinical data	NAC invasion [*n* (%)]		Tests	*P* value (significance)
	Absent (*N*=50)	Present (*N*=11)		
Patient's complaint				
Painless lump				
Absent	18 (36)	7 (63.6)	2.847[a]	0.174 (NS)
Present	32 (64)	4 (36.4)		
Painful lump				
Absent	36 (72)	9 (81.8)	0.449[a]	0.711 (NS)
Present	14 (28)	2 (18.2)		
Axillary lump				
Absent	48 (96)	11 (100)	0.455[a]	0.500 (NS)
Present	2 (4)	0 (0)		
Nipple discharge				
Absent	49 (98)	11 (100)	0.224[a]	1.000 (NS)
Present	1 (2)	0 (0)		
Bleeding per nipple				
Absent	50 (100)	10 (90.9)	4.621[a]	0.180 (NS)
Present	0 (0)	1 (9.1)		
Nipple retraction				
Absent	49 (98)	7 (63.6)	14.149	0.003 (S)
Present	1 (2)	4 (36.7)		
Breast size (bra size)				
Mean±SD	42.48±2.47	43.63±2.65	−1.321[b]	0.186 (NS)
Median (range)	42 (38–46)	44 (40–46)		
Bilaterality				
No	50 (100)	9 (90)	5.085[a]	0.167 (NS)
Yes	0 (0)	1 (10)		
Focality				
Unifocal	50 (100)	2 (18.2)	47.990[a]	<0.001 (HS)
Multifocal	0 (0)	9 (81.8)		

HS, highly significant; NAC, nipple–areola complex; S, significant. [a]χ^2-test. [b]Mann–Whitney *U*-test. $P<0.05$, significant.

Table 3 Site of the tumour of the studied groups

Tumour site	NAC invasion [*n* (%)]		Tests	*P* value (significance)
	Absent (*N*=50)	Present (*N*=20)		
Nonpalpable				
No	50 (100)	18 (90)	5.147[a]	0.079 (NS)
Yes	0 (0)	2 (10)		
Upper outer 1/4				
No	16 (32)	12 (60)	4.667[a]	0.081 (NS)
Yes	34 (68)	8 (40)		
Upper inner 1/4				
No	44 (88)	19 (95)	0.778[a]	0.664 (NS)
Yes	6 (12)	1 (5)		
Lower outer 1/4				
No	44 (88)	20 (100)	2.625	0.173 (NS)
Yes	6 (12)	0 (0)		
Lower inner 1/4				
No	47 (94)	18 (90)	0.345	0.619 (NS)
Yes	3 (6)	2 (10)		
Central				
No	50 (100)	14 (70)	16.406	<0.001 (HS)
Yes	0 (0)	6 (30)		
Axillary tail				
No	49 (98)	19 (95)	0.463	0.493 (NS)
Yes	1 (2)	1 (5)		

HS, highly significant; NAC, nipple–areola complex. [a]χ^2-test. $P<0.05$, significant.

Table 4 Size of the tumour (cm) of the studied groups

Size of the tumour (cm)	NAC invasion		Test	*P* value (significance)
	Absent (*N*=50)	Present (*N*=20)		
Clinical				
Mean±SD	3.30±1.13	2.85±1.30	–0.839•	0.401 (NS)
Median (range)	3 (1.50–6)	3 (0–4.50)		
Ultrasound				
Mean±SD	2.60±1.01	2.57±0.81	–0.205•	0.838 (NS)
Median (range)	2.50 (1–6)	3 (1–4)		

NAC, nipple–areola complex. •Mann–Whitney *U*-test. ‡Chi-square (χ^2) test. $P<0.05$, significant.

Table 5 Distance from mass to nipple in the studied groups

Variable	NAC invasion		Test	*P* value (significance)
	Absent (*N*=50)	Present (*N*=20)		
Distance from mass to nipple				
Mean±SD	7.24±2.73	3.15±2.80	–5.320•	<0.001 (HS)
Median (range)	6 (4.50–16)	2.75 (0–12)		

NAC, nipple–areola complex. •Mann–Whitney *U*-test. ‡Chi-square (χ^2) test. $P<0.05$, significant.

Table 6 Histopathological examination of the studied groups

Histopathological examinations	NAC invasion [*n* (%)]		Test	*P* value (significance)
	Absent (*N*=50)	Present (*N*=11)		
Histopathology of MRM				
IDC	42 (84)	10 (90.9)	0.944‡	0.624 (NS)
ILC	4 (8)	0 (0)		
IDC+ILC	4 (8)	1 (9.1)		
Histopathological grade				
Grade I	0 (0)	0 (0)	9.350‡	0.002 (S)
Grade II	30 (60)	1 (9.1)		
Grade III	20 (40)	11 (90.9)		
Lymph node				
Node negative	20 (40)	0 (0)	6.546‡	0.011 (S)
Node positive	30 (60)	11 (100)		

IDC, invasive duct carcinoma; ILC, invasive lobular carcinoma; MRM, modified radical mastectomy; NAC, nipple–areola complex; S, significant. ‡χ^2-test. $P<0.05$, significant.

Table 7 Biological markers of the studied groups

Biological markers	NAC invasion [*n* (%)]		Test	*P* value (significance)
	Absent (*N*=50)	Present (*N*=11)		
ER				
Negative	9 (18)	10 (90.9)	22.349[a]	<0.001 (HS)
Positive	41 (82)	1 (9.1)		
PR				
Negative	12 (24)	8 (72.7)	9.715[a]	0.004 (S)
Positive	38 (76)	3 (27.3)		
HER2/neu overexpression				
Negative	46 (92)	1 (9.1)	35.049[a]	<0.001 (HS)
Positive	4 (8)	10 (90.9)		

ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2; NAC, nipple–areola complex; PR, progesterone receptor; S, significant. [a]χ^2-test. $P<0.05$, significant.

The main benefits of NSM are oncological safety, preservation of inframammary fold and breast contour, absence of skin colour differences as in flaps, better cosmetic result, sensation of integrity and positive psychological effects related to the nipple preservation [9]. In this study, NAC involvement was noted in nine of 60 mastectomy specimens. Therefore, the incidence of occult NAC involvement was 15%. This rate indicates that even patients who had clinically normal-appearing NAC should be carefully selected for NAS

mastectomy. This falls in the same range reported by Gomez *et al*. [10], who reported that the incidence of NI ranges from 0 to 58%.

In this study, there was no statistically significant association between age groups and NAC invasion (P=0.121) and this matches with Zhang *et al.* [7].

In this study, there was no statistically significant association between menstrual state and NAC invasion (P=0.558). This coincides with Abou Nagah and El-Sabaa [11].

In this study, there was no statistically significant association between family history and NAC invasion (P=1.000).

In this study, the most common patient complaint was painless lump (58.3%), painful lump (26.7%) and nipple retraction (8.3%). There was a statistically significant association between nipple retraction and NAC invasion (P=0.003) .Other patient's complaints had no statistically significant association with NAC invasion, such as painless lump (P=0.174), painful lump (P=0.711), axillary lump (P=0.500) and bleeding per nipple (P=0.180).

In this study, there was no statistically significant association between breast size (measured using the bra size) and NAC invasion (P=0.186) and this matches with Abou Nagah and El-Sabaa [11].

In this study, there was a statistically highly significant association between focality and NAC invasion (P<0.001). This is in agreement with Zhang *et al.* [7], Wang *et al.* [12] and Weidong *et al.* [13], who suggested that patients with multifocal or multicentric tumours are at a higher risk to have NI, and this is in disagreement with Brachtel *et al*. [14], who found no significant association between multifocal tumours and NAC invasion.

There was a highly significant association between centrally located tumours and NAC invasion, as tumours located in the central areas are more likely to have nipple invasion (NI) compared with peripheral areas (P<0.001). This is in agreement with Wang *et al.* [12], Weidong *et al.* [13], Khan *et al.* [15], Gulben *et al.* [16] and Simmons *et al.* [17].

In this study, there was no statistically significant association between tumour size neither clinically assisted or ultrasound-assisted and NAC invasion (P=0.401 and 0.838). This is in agreement with Loewen *et al.* [18], Schecter *et al.* [19] and Vlajcic *et al*. [20], whose results failed to show any statistically significant association between tumour size and occult NI. This differs from the findings of Zhang *et al*. [7], who reported that the risk for NAC invasion increased significantly in patients with larger tumours.

In this study, there was a statistically highly significant association between the tumour–nipple distance and NAC invasion (P<0.001). This was reported by Weidong *et al*. [13], Brachtel *et al*. [14] and Vlajcic *et al*. [20].

In our study, the optimum cutoff of distance from mass to nipple as a predictor for NAC invasion in breast carcinoma was less than or equal to 4 cm. Therefore, all tumours with distance more than 4 cm from the nipple are expected less likely to have NAC invasion. Therefore, we can conclude that a distance more than 4 cm is needed for NAS mastectomy. This coincides with the finding of Vlajcic *et al*. [20], who found that the NAC could be safely preserved with tumour-to-nipple distance more than 4 cm. This differs from Zhang *et al*. [7], who suggested that a distance of 2.5 cm from the tumour to the nipple is required to reduce the risk for NI.

In our study, there was no statistically significant association between histological type of the tumour and NAC invasion (P=0.624). This is in agreement with Zhang *et al*. [7] and in disagreement with Brachtel *et al*. [14], who found a significantly higher incidence of NI in invasive ductal carcinoma tumours with an extensive intraductal component.

In this study, there was a statistically significant association between histological grade of the tumour and NAC invasion (P=0.002). This is in agreement with Eisenberg *et al*. [21] and Pirozzi *et al*. [22]; however, it differs from Gulben *et al*. [16] and Simmons *et al*. [17], who found no significant association in rates of NAC invasion and tumour grades.

In this study, there was a statistically significant association between positive lymph node invasion and nipple invasion (P=0.001). This coincides with the finding of Mallon *et al*. [23], but in disagreement with the findings of Simmons *et al*. [17], who did not show a higher incidence of NAC invasion in the lymph node positive group.

In this study, there was no statistically significant association between tumour stage and NAC invasion (P=0.342). This is in disagreement with Zhang *et al.* [7], who suggested that patients with stage III and IV diseases were found to be at significantly higher risk for NAC invasion than those with stage I and II diseases.

In our study, there was a statistically highly significant association between ER negativity and NAC invasion, in which 18% of patients without NAC invasion had negative ER versus 90.9% of patients with NAC invasion (P<0.001).

In our study, there was a statistically highly significant association between HER2 positivity and NAC invasion (P<0.001), and this is in agreement with Zhang *et al.* [7], who suggested that patients with positive (HER2) have a higher rate of NAC invasion.

In our study, the incidence of occult nipple malignancy increased with tumour-to-nipple distance less than 4 cm, lymph node metastasis, LVI, HER2 amplification, multicentricity and retroareolar location, and this matches with Mallon *et al.* [23]. However, it is in disagreement with Wang *et al.* [12], who found that NAC involvement is strongly associated with tumour size and the expression levels of ER and PR were not associated with NAC involvement.

According to our study, the ideal patients for NAS mastectomy should have the following criteria: clinically normal NAC, tumour–nipple distance more than 4 cm, no multicentric tumour, absence of lymph node involvement, peripheral and not central tumour and absence of subareolar tumour involvement (LVI). This coincides with Kim *et al.* [24], Gerber *et al.* [25], Petit *et al.* [26], Benediktsson and Perbeck [27] and Simmons *et al.* [17].

Conclusion

According to our study NAS mastectomy is ideal for patients fulfilling the following criteria:

(1) Clinically normal NAC
(2) Tumour–nipple distance more than 4 cm.
(3) No multifocal/multicentric tumour.
(4) No lymph node invasion.
(5) Tumour grade I or II.
(6) Peripheral and not central tumour.
(7) No LVI.
(8) ER receptor positive.
(9) PR receptor positive.
(10) HER2 negative.

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Conflicts of interest

There are no conflicts of interest.

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