
Evaluation of Nipple-Areola Complex (NAC) involvement in Breast Carcinoma

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Abstract:

Objective: This study was undertaken to find the frequency and factors affecting the nipple-areola complex (NAC) in breast carcinoma so as to find the feasibility of nipple-sparing mastectomy (NSM) in the management of breast carcinoma.

Patients and Methods: This study was conducted in Department of Surgery, Tobruk Medical Center, Tobruk, Libya from October 2003 to February 2007. 25 Libyan female patients with carcinoma breast were included in this study. Patients with clinical NAC involvement e.g. ulceration (Paget's disease), fixation or induration were excluded, whereas those with nipple retraction or discharge were included in the study. All patients were subjected to modified radical mastectomy. Nipple-areola biopsy was done to find its involvement. The NAC was considered involved with malignancy, if the tumor infiltration was within 5 mm of the NAC.

Results: In the present study, out of 25 cases, 3 (12%) showed pathological NAC involvement. NAC involvement was significantly associated with centrally located tumors ($P = 0.029$), tumors with nipple retraction ($P = 0.029$) and tumors with skin involvement ($P = 0.029$). NAC involvement was not associated with age ($P = 1.000$), laterality of tumor ($P = 1.000$), tumor size ($P = 1.000$), tumor grade ($P = 0.252$), or axillary lymph nodes ($P = 0.543$).

Conclusion: Nipple-sparing mastectomy may be suitable for selected cases of breast carcinoma with low probability of nipple involvement by carcinoma.

Key Words: Nipple-sparing mastectomy, NAC, Nipple-Areola Complex, Carcinoma Breast

Introduction:

The surgical treatment of breast cancer over the past century has evolved from extensive disfiguring procedures to less invasive and cosmetically acceptable ones. Radical mastectomy remained the corner stone for the treatment of breast cancer for about first three-quarter of the twentieth century. After that, many surgeons regarded radical mastectomy as too debilitating and several centers were reporting good outcome with less extensive surgery. These procedures include modified radical mastectomy and breast-conserving therapy (BCT).¹

In the absence of skin, nipple or chest involvement, BCT is considered the preferred treatment for early breast cancer. Several studies have shown equal survival and local control in BCT compared with mastectomy.²⁻⁴ In women with breast cancer, for whom BCT is not the best option, a nipple-sparing mastectomy (NSM) has been proposed as a good and safe alternative to conventional, more radical mastectomy. In NSM, the breast skin and nipple-areola complex (NAC) are

preserved with intra-operative pathological assessment of the nipple tissue core, and immediate reconstruction, therapy permitting cosmeses for patient mastectomy.⁵

Surgeons hesitate to perform NSM, for fear of recurrence of tumor in the NAC due to undetected nipple involvement of the tumor. Many surgeons believe that it is essential to remove the NAC when a mastectomy is performed because of the presumed risk of cancer involvement by intra-ductal or lymphatic spread into the nipple. This classical dogma might be related to the work of Sappey,⁶ who described more than 100 years ago, that the lymphatic drainage of the breast is centripetal towards the sub areolar plexus. However studies by Turner-Warwick⁷ and Handly⁸ had proved that, lymphatic drainage of the breast is downward towards the deep pectoral lymphatic plexus.

Several authors have claimed to perform NSM with good cosmetic results, acceptable recurrence rates and high patient satisfaction.⁹⁻¹³

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Still this operation is not widely accepted as a viable option. This study was done to find the frequency and factors affecting NAC involvement so as to find the feasibility of NSM in the management of breast carcinoma.

Patients and Methods:

25 Libyan female patients, with operable breast carcinoma, admitted to the Department of Surgery, Tobruk Medical Center, Tobruk, Libya between October 2003 to February 2007 were included in this study. Patients with clinical NAC involvement e.g. nipple ulceration (Paget's disease), fixation or in duration of nipple were excluded, whereas those with nipple retraction or discharge were included in the study.

Every patient was subjected to detailed history and general examination. Local examination of breast mass, nipple changes, areolar changes, skin changes and nodal status were done. All patients were subjected to bilateral mammography and complementary ultrasonographic examination of both breasts and axilla were done to define the criteria of the primary tumor. Chest X- ray was done to exclude pulmonary metastases. C.T scan of the chest was done if the plain X-ray film demonstrated any suspicious lesion. Ultrasound of abdomen was done to exclude abdominal metastases. C.T scan of the abdomen was done when needed e.g. associated ovarian lesion, suspicious lesion in the liver.

Fine needle aspiration cytology of the tumor was done to confirm the diagnosis. If the result was not conclusive, excisional biopsy of the

tumor was done to establish a histopathological diagnosis.

All patients were subjected to modified radical mastectomy. Surgical specimens were bisected in its biggest dimension to measure maximum histological diameter, and to compare with clinical, mammographic and ultrasonic diameters. Histopathological examination of the tumor was done to evaluate the pathological type, grade and stage of tumor. Nipple-areola biopsy was done to find NAC involvement. The routine technique of cutting the nipple and areola while examining a mastectomy specimen included three parallel cuts made at random perpendicular to the plane of the skin in the nipple and areola. When a lesion was visible on these either of structures, the cuts were made transversely across it at different levels. The NAC was considered involved with malignancy if the tumor infiltration was within 5 mm of the NAC.

The collected data were tabulated and statistically analyzed using SPSS software statistical computer version 12. Fischer exact test was used as a test of significance. Significance was adopted at $P < 0.05$ for interpretation of results of tests of significance.

Results:

The age of the patients ranged from 34-60 years, with a median of 45years. In 12% (3 out of 25 patients), there was NAC involvement by carcinoma, as demonstrated pathologically.

Age ($P = 1.000$) Table 1, and laterality of tumor (right or left breast) ($P = 1.000$) Table 2 was not associated with NAC involvement.

Table 1: NAC involvement in relation to age.

Age	NAC involvement		No of patients
	Negative	Positive	
≤ 45 yrs	11	1	12
> 45 yrs	11	2	13
P value	1.000		25

Table 2: NAC involvement in relation to laterality of tumor.

Site of tumor	NAC involvement		No of patients
	Negative	Positive	
Right breast	10	1	11
Left breast	12	2	14
P value	1.000		25

Location of the tumor is a variable that predicted NAC involvement. Centrally located tumors had a higher incidence of NAC

involvement (66.7%) than peripherally located tumors (4.5 %) ($P = 0.029$) Table 3.

Table 3: NAC involvement in relation to tumor location.

Tumor location	NAC involvement		No of patients
	Negative	Positive	
Central	1	2	3
Peripheral	21	1	22
P value	0.029		25

In the present study tumor size (P = 1.000)
Table 6, grade of tumor (P = 0.252) Table 7
and positive axillary lymph nodes (P = 0.543)

Table 8, were not associated with NAC involvement.

Table 4: NAC involvement in relation to tumor size.

Size of tumor	NAC involvement		No of patients
	Negative	Positive	
≤ 2 cm	11	1	12
> 2 cm	11	2	13
P value	1.000		25

Table 5: NAC involvement in relation to tumor grade.

Tumor grade	NAC involvement		No of patients
	Negative	Positive	
Poorly differentiated	3	2	5
Well differentiated	17	3	20
P value	0.252		25

Table 6: NAC involvement in relation to axillary lymph nodes.

Lymph node involvement	NAC involvement		No of patients
	Negative	Positive	
≤ 4 lymph nodes	14	1	15
> 4 lymph nodes	8	2	10
P value	0.543		25

NAC involvement was associated with clinical nipple involvement. NAC involvement was more in cases with nipple retraction (66.7%)

than in cases without nipple retraction (4.5%) (P = 0.029) Table 7.

Table 7: Pathological NAC involvement in relation to nipple retraction

Clinical nipple involvement	Pathological NAC involvement		No of patients
	Negative	Positive	
Nipple retraction	1	2	3
Normal nipple	21	1	22
P value	0.029		25

Tumors with skin involvement were associated with NAC involvement. (66.7% in tumors with

skin involvement, 4.5% in tumors without skin involvement, P = 0.029) Table 8.

Table 8: NAC involvement in relation to skin involvement.

Skin involvement	NAC involvement		No of patients
	Negative	Positive	
Absent	21	1	22
Present	1	2	3
P value	0.029		25

Discussion:

Surgical treatment of breast carcinoma traditionally included resection of the NAC. Objection to NAC preservation stems from the widely held belief that the lymphatic drainage of the breast passes to the subareolar plexus of **Sappey**, before distribution to the axillary or internal mammary chain. This theory was discredited by Turner and Warwick⁷ using vital staining techniques and radiography. They proved that the majority of lymphatic channels accompany blood vessels and permeate through the substance of the breast without any significant relay to the nipple area. The explanation of this discrepancy is that, Sappey's original studies were carried out in lactating breast rather than resting breast.⁶

The trend in the surgical treatment of breast cancer has become more conservative. Although BCT has been shown to be an oncologically sound strategy for most early stage breast cancer, mastectomy remains the treatment of choice for many women, either because of patient preference or because of tumor characteristics that are not compatible with the conservative approach.¹⁴

Randomized controlled trials comparing mastectomy with BCT have shown no difference in either overall or disease free survival. The problem remains as to do the best treatment for patients without subsequent local recurrence, which is more common after BCT.³ However, BCT preserves the breast, including the NAC and so maximizes the benefits of both cancer treatment and cosmetic outcome while minimizing risks.¹⁴

Skin-sparing mastectomy (SSM) is regarded as a major improvement in breast reconstruction over the past couple of decades. It removes the breast, nipple-areola complex, previous biopsy incisions, and skin overlying superficial tumors. By preserving most of the skin of the native chest wall, the plastic surgeon is able to reconstruct a more symmetrical breast with preservation of the sub mammary fold and breast contour.¹⁵

NAC typically has been included in the mastectomy, because of that cosmetic approaches have involved nipple-areola reconstruction. In most patients, small flaps of skin from breast mound are used for the nipple, while the areola is simulated by means of tattooing. Although this approach can give

excellent cosmetic results, there are potential disadvantages. The use of surrounding skin flaps for reconstruction can lead to a nipple with little or no sensitivity, pale color, and possible loss of projection as the scars soften over time. All these techniques produce a cosmetic result inferior to that of real nipple itself.¹⁶

So preservation of the NAC offers the possibility of preserving sensitivity and providing a good cosmetic match to the contra lateral breast. This approach could be recommended only if there were a reasonable certainty that no occult tumor was located at the NAC site.¹⁷

Little is known about the presence of microscopic tumor in the NAC. In fact, this type of neoplastic involvement has been rarely studied, and the available few reports on this problem show a variable frequency ranging from 0%-50%. These disparities arise because of the different techniques used for histological examination of NAC specimens and different selection criteria.

Pathological NAC involvement in this study was 12% (3 out of 25 cases) and this figure is comparable with that reported by Crowse et al.⁵ which was 12%. Raafat and Ali study in Egypt reported an incidence of 6.3%, while Simmons et al. reported an incidence of 10.6%. The highest incidence of NAC involvement (50%) was reported by Andersen and Pallesen,¹⁸ while the lowest (0%) was reported by Hudson et al.¹⁹

Location of the breast cancer is a variable that predicted NAC involvement. Morimoto et al.²³ believed that centrally located tumors have a high possibility of infiltrating NAC. In our study, the incidence of NAC involvement was 66.7% in centrally located tumor and 4.5% in peripherally located tumors ($P = 0.029$). Galimberti et al.²⁴ found an incidence of 54.1% in centrally located tumors and 6.4% in peripherally located tumors. Simmons et al.²¹ reported 27.3% and Chiu et al.¹⁵ reported 91% NAC involvement in centrally located tumors. Many studies concluded that, higher stage tumors have a greater risk of nipple involvement because of generally larger size tumor.²⁰ In the current study NAC involvement was documented in 15.4% cases with tumor size > 2 cm, whereas in tumor ≤ 2 cm it was

8.3%, but it was not statistically significant ($P=1.000$). Simmons et al.²¹ reported an incidence of 8.9 % in tumors > 2 cm and 12.1% in tumors < 2 cm ($P=0.45$), whereas Raafat and Ali²² reported a higher incidence of NAC involvement in tumors more than > 3 cm.

Some studies reported that the degree of differentiation of the tumor might affect the incidence of cancerous nipple involvement. Smith et al.²⁵ found an incidence of 37% NAC involvement in poorly differentiated tumors. Lagios et al.²⁶ demonstrated two fold increase in nipple involvement in poorly differentiated tumors. Our study shows that poorly differentiated tumors have a higher incidence (40%) of pathological NAC involvement, than well differentiated tumors (15%) but it was not statistically significant ($P=0.252$).

In present study, there was a higher incidence of NAC involvement in cases with > 4 axillary lymph nodes (20%), than in cases with ≤ 4 axillary lymph nodes (6.7%) but it was not statistically significant ($P=0.543$). Simmons et al.²¹ reported an incidence of 14.3% and 3.4% in patients with > 2 axillary nodes and in patients with ≤ 2 axillary lymph nodes respectively.

Another reliable variable is nipple retraction. In this study pathological NAC involvement was seen in 66.7 % of cases with nipple

retraction, while in normal nipple it was 4.5% ($P=0.029$). This was supported by Chiu et al.¹⁵ and Raaafat and Ali²² who reported an incidence of 87.5% and 80% NAC involvement in cases with nipple retraction respectively.

NAC involvement showed correlation with skin involvement in the form of peau d'orange or skin ulceration. Tumors with skin involvement had a higher incidence (66.7%) of NAC involvement than tumors without skin involvement (4.5%) ($P=0.029$). This finding is supported by Raafat and Ali²² where NAC involvement was 25.8% in cases with skin involvement and 2.8% in cases without skin involvement ($P=0.0001$).

Conclusion:

This study shows that in breast carcinoma, nipple-areola complex (NAC) involvement is associated with location of tumor in breast, skin involvement and clinical nipple involvement.

Involvement of NAC has a strong implication for adequate treatment of breast cancer if it is preserved. The fore mentioned results of the present study, compared with those of other studies, suggest that nipple-sparing mastectomy (NSM) could be an option for carefully screened patients.

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