Predictive value of axillary nodal mapping after neoadjuvant chemotherapy in breast cancer

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Received 15 December 2015
Accepted 16 December 2015

The Egyptian Journal of Surgery
2016, 35:106–111

Purpose
The aim of the study was to determine the feasibility and accuracy of sentinel lymph node biopsy (SLNB) in patients with advanced breast cancer after preoperative chemotherapy.

Patients and methods
A prospective study was conducted on 73 patients with advanced operable breast carcinoma previously treated with preoperative chemotherapy. Sentinel lymph node (SLN) mapping was performed at the time of surgery. Following surgery all patients received comprehensive postoperative radiotherapy at 50 Gy/5 weeks.

Results
Seventy-three patients with a median age of 52 years who had been previously treated with preoperative chemotherapy at Menofia University Hospital and National Cancer Institute (NCI) between May 2006 and May 2013 were selected for this study. The SLN detection rate was 79.5%. Thirty-three of 58 patients (56.9%) had successfully mapped positive SLNs. The false-negative rate was 22.4%.

Conclusion
This study confirms the feasibility of SLNB after preoperative chemotherapy in the case of advanced operable breast cancer. According to the detection rate and false-negative rate SLNB may predict metastatic disease in the axilla of patients with tumor response following preoperative chemotherapy.

Keywords:
advanced breast cancer, neoadjuvant chemotherapy, sentinel lymph node biopsy

Egyptian J Surgery 35:106–111
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1110-1121

Introduction

Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer among women aged 20–59 years. It accounts for 26% of all newly diagnosed cancers in women and is responsible for 15% of cancer-related death in them [1]. The three most common pathological types of breast cancers are invasive mammary (ductal) carcinoma (75%), ductal carcinoma *in situ* (13%), and invasive lobular carcinoma (5%) [2].

Axillary staging is performed in all patients with invasive breast cancer. Axillary lymph node status is the most prognostic factor in patients with invasive breast cancer. Identifying patients with axillary lymph node metastases has important implications as regards prognosis, regional treatment, and local control [3].

Neoadjuvant chemotherapy (NAC) is being increasingly used in the management of patients with large (T2) and locally advanced (T3, T4, or N2) breast cancers. Such treatment is administered with the aim of reducing the size of the primary tumor to increase the likelihood of breast conservation and to treat occult systemic metastases to improve survival [4]. NAC downstages 20–40% of pretherapy documented axillary metastatic lymph nodes, with a complete pathologic response in 32% [5].

Sentinel lymph node biopsy (SLNB) has become a validated technique that replaced axillary lymphadenectomy for axillary staging in patients with early breast cancer (N0) and is associated with less morbidity [6]. SLNB after NAC may predict axillary lymph node status for patients with clinically negative lymph node status following NAC. This procedure could help patients who have had their axillary lymph node status downstaged from positive to negative, and patients with large tumors qualify as appropriate candidates for SLNB [7].

After NAC, the method of choice with mastectomy or breast conservative surgery (BCS) is level I and level II axillary lymphadenectomy [8]. SLNB provides a

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minimally invasive approach to detect lymph node metastases, thus defining a group of lymph node-negative patients who may be spared the morbidity associated with an axillary lymph node dissection [9].

Patients and methods

The study included 105 patients with breast cancer admitted for NAC at Menofia University Hospital and National Cancer Institute (NCI) between May 2006 and May 2013 after obtaining approval from the Ethical Committee of the Faculty of Medicine, Menofia University, and National Cancer Institute. Their primary nodal status was as follows: 70 cases with N1 status and 35 cases with N2 status. Reassessment after NAC revealed 32 cases with N1 nodal stage and 73 patients with N0 stage. This prospective study was conducted on the latter 73 patients; they were classified as stage II or III according to the American Joint Committee on Cancer (AJCC). NAC consisted of three courses of NAC (TAC: docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2).

All patients underwent routine workup including the following:

(1) Full history taking, general and local examination, routine laboratory investigations, and full metastatic workup.
(2) Fine needle aspiration cytology or Tru-cut needle biopsy for pathological assessment and for detecting ER, PR, and Her2 status for every patient.

Inclusion criteria included the presence of operable, noninflammatory, large breast tumor diagnosed by fine-needle aspiration cytology or core needle biopsy and treated with NAC. Axillary status was clinically free of nodes (N0). Patients with inflammatory cancer, clinically fixed axillary lymph nodes, previous breast surgery (even excisional biopsy), and premature interruption of NAC for cancer progression were excluded from the study.

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Lymphatic mapping procedure

In all patients, definitive surgical therapy through BCS or mastectomy and axillary dissection was done. Sentinel lymph node (SLN) mapping was performed at the time of surgery; all patients were injected with 1 ml of 1% patent blue dye peritumorally at 12, 3, 6, and 9 o'clock (total 4 ml) into the breast parenchyma. Gentle massage was performed for 10–15 min before axillary incision and sentinel node identification, followed by completion of axillary lymphadenectomy.

Pathologic analysis

No intraoperative histopathologic examination was performed. SLNs were submitted by the surgeons separately from other axillary lymphadenectomies. The microscopic report stated the number of axillary SLNs, the total number of nodes, and the number of nodes containing macrometastasis or micrometastasis (sentinel and nonsentinel) using the definition of the last AJCC staging system.

Radiotherapy

After surgery all patients received comprehensive radiotherapy to the intact breast or to the chest wall in case of mastectomy and to the supraclavicular lymph node at a dose of 50 Gy/25 fractions/5 weeks followed by a booster dose of 10 Gy/5 fractions to the tumor bed in breast cancer patients who had undergone BCS and those who were less than 60 years old.

Studied parameters

Clinical breast tumor size and axilla assessment were obtained before any treatment by physical examination. The detection rate was defined as the number of patients whose axillary SLN was successfully identified in relation to the total number of patients included.

The average number of SLNs collected was calculated according to the SLN definition. The false-negative rate of SLN was defined as the proportion of patients with a negative SLNB among those with positive nonsentinel nodes. The false-positive rate of SLN was defined as the proportion of patients with a positive SLNB among those with negative nonsentinel nodes. Accuracy was defined as the ratio of patients in whom SLNB correctly diagnosed axillary lymph node status. The results of the detection rate and false-negative rate were stratified according to clinical tumor characteristics.

Statistical analysis

Data were analyzed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, Illinois, USA). The χ^2-test (Fisher's exact test) was used to examine the relation between qualitative variables. The

κ-test was used as a measure of agreement between SLNB results and axillary of nonsentinel nodes. A *P* value less than 0.05 was considered significant.

Results

The mean age of the involved 73 patients was 49.0 ± 9.3 years (range: 32–38 years). Tumor characteristics before and after chemotherapy are summarized in Table 1. Management comprised BCS in 44 patients (60.3%) and modified radical mastectomy in 29 (39.7%). NAC significantly downstaged tumor size in 75.3% of cases ($P < 0.001$) and nodal stage in 70% of cases ($P < 0.001$). The SLN detection rate was 71.2% (52 out of 73 cases were successfully mapped). The number of SLNs per patient ranged from one to four nodes. No complications were observed as a result of dye injection in any of the patients.

Table 2 shows factors affecting the success of SLN mapping. The only factor associated with successful SLN mapping was tumor site. The success rate was higher in tumors involving the outer breast quadrant compared with the lower quadrant ($P < 0.001$). Clinical T-stage, N-stage before NAC, and positive lymphovascular invasion were not related to the success of mapping.

The number of positive SLNs was 29/52 (55.8%). Table 3 shows the relation between SLN positivity and tumor characteristics. SLN positivity was not affected by any tumor characteristic, including initial nodal status.

After definitive surgical treatment and pathological examination of axillary nodes, 30 patients (57.7%) were seen to have positive nonsentinel nodes and 22 (42.3%) had negative nodes. Positive SLN correctly predicted 18/30 of the positive nonsentinel nodes – that is, a false-negative rate for SLN of 40%. Negative SLN correctly predicted 11/22 of the negative nonsentinel nodes – that is, a false-positive rate for SLN of 50%. Generally, accuracy of SLN was 55.8%; 29 out of 52 cases were correctly diagnosed (κ-value of 0.099; i.e. no agreement between the two tests) (Table 4).

Table 1 Tumor characteristics of the studied group

	No.	%
Tumor Site		
UOQ	34	46.6
LOQ	11	15.1
LIQ	10	13.7
UIQ	14	19.2
Contralateral	4	5.5
Pathological Type		
IDC	61	83.6
ILC	8	11.0
Mixed	4	5.5
T-Stage before NAC		
T2	23	31.5
T3	45	61.6
T4	5	6.8
Grade		
I	3	4.1
II	38	52.1
III	32	43.8
N-Stage before NAC		
N1	50	68.5
N2	23	31.5
Lymphovascular invasion		
Yes	21	28.8
No	52	71.2
Ultrasound of LNs		
Suspicious	46	63.0
Malignant	24	32.9
Normal	3	4.1
T-Stage after NAC		
T1	17	23.3
T2	44	60.3
T3	11	15.1
T4	1	1.4

Discussion

This study demonstrated a 40% false-negative rate of SLN pathology in cases with locally advanced breast cancer following NAC. Positive SLN correctly identified only 18 out of 30 cases with positive nonsentinel nodes. False-positive rate of SLN was even higher (50%). There was no agreement between SLN and nonsentinal nodal pathological findings (κ=0.099). SLN showed accuracy of 55.8% in predicting non-SLN status. SLN positivity was not affected by preneoadjuvant nodal status ($P = 0.157$). In this group of advanced breast cancer patients, mapping of SLN was successful in 71.2% of cases. We did not record any complications as a result of dye injection in any of the patients.

The main hypotheses to explain axillary mapping failures after NAC are an alteration of the lymphatic pathway owing to fibrosis of lymphatic channels, the potential obstruction of lymphatic channels with cellular material or tumor emboli, fibrosis of lymph vessels, and a fatty degeneration owing to the apoptosis of tumor cells [10]. However, in a retrospective analysis of 192 patients who had undergone axillary lymph node dissections and NAC, Straver *et al.* [11] confirmed the feasibility and even importance of adequate lymph node dissection to provide precise prognostic information.

To avoid difficulties resulting from pathologic modifications of the lymphatic pathway secondary

Table 2 Tumor characteristics and their relation with success of SNL mapping

	Sentinel lymph node mapping (%)		*P* value
	Success (*n*=52)	Failure (*n*=21)	
Tumor site			
UOQ	28 (82.4)	6 (17.6)	
LOQ	8 (72.7)	3 (27.3)	< 0.001
LIQ	10 (10.0)	0 (0.0)	
UIQ	2 (14.3)	12 (85.7)	
Contralateral	4 (100.0)	0 (0.0)	
Pathological type			
IDC	41 (67.2)	20 (32.8)	0.265
ILC	7 (87.5)	1 (12.5)	
Mixed	4 (100.0)	0 (0.0)	
T-Stage before NAC			
T2	17 (73.9)	6 (26.1)	0.322
T3	33 (73.3)	12 (26.7)	
T4	2 (40.0)	3 (60.0)	
Grade			
I	2 (66.7)	1 (33.3)	0.822
II	26 (68.4)	12 (31.6)	
III	24 (75.0)	8 (25.0)	
N-Stage before NAC			
N1	33 (66.0)	17 (34.0)	
N2	19 (82.6)	4 (17.4)	0.145
Lymphovascular invasion			
Yes	12 (57.1)	9 (42.9)	0.152
No	40 (76.9)	12 (23.1)	
Ultrasound of LNs			
Suspicious	31 (67.4)	15 (32.6)	
Malignant	18 (75.0)	6 (25.0)	0.589
Normal	3 (100.0)	0 (0.0)	

Table 3 Relation between SNL positivity and tumor characteristics

	Pathology sentinel (%)		*P* value
	Positive (*n*=29)	Negative (*n*=23)	
Tumor site			
UOQ	21 (75.0)	7 (25.0)	
LOQ	3 (37.5)	5 (62.5)	*
LIQ	3 (30.0)	7 (70.0)	
UIQ	2 (100.0)	0 (0.0)	
Contralateral	0 (0.0)	4 (100.0)	
Pathological type			
IDC	26 (63.4)	15 (36.6)	*
ILC	2 (28.6)	5 (71.4)	
Mixed	1 (25.0)	3 (75.0)	
T-Stage before NAC			
T2	10 (58.8)	7 (41.2)	1.000
T3	18 (54.5)	15 (45.5)	
T4	1 (50.0)	1 (50.0)	
Grade			
I	0 (0.0)	2 (100.0)	0.237
II	14 (53.8)	12 (46.2)	
III	15 (62.5)	9 (37.5)	
N-Stage before NAC			
N1	21 (63.6)	12 (36.4)	
N2	8 (42.1)	11 (57.9)	0.157
Lymphovascular invasion			
Yes	7 (58.3)	5 (41.7)	1.000
No	22 (55.0)	18 (45.0)	
Ultrasound of LNs			
Suspicious	17 (54.8)	14 (45.2)	
Malignant	9 (50.0)	9 (50.0)	0.343
Normal	3 (100.0)	0 (0.0)	

to NAC, some authors suggested performing SLNB before NAC. According to this strategy, women with involved SLNs before NAC must undergo axillary lymphadenectomy after NAC. This strategy has two main disadvantages: first, each woman with involved SLNs will experience two separate axillary surgical procedures, before and after NAC; second, women with lymph node metastasis at presentation, eradicated by NAC, will undergo an unnecessary lymphadenectomy. SLNB performed after NAC eliminates the need for two axillary surgical procedures in patients with involved sentinel nodes, and may avoid a systematic axillary lymphadenectomy in the case of lymph node downstaging [12].

The methods of SLN detection have an impact on both the detection rate and the false-negative rate [13]. Sentinel node identification using blue dye alone is a difficult technique to learn and requires a wider exposure of the surgical wound to trace the afferent lymphatics to the tail of the breast. Meta-analysis showed that SLN identification rate is lower and the false-negative rate higher than when using radiocolloid in isolation or a combination of techniques [14].

To reduce the SLNB false-negative rate after NAC, an axillary intraoperative ultrasound assessment after SLNB to explore the nonsentinel region for additional suspicious lymph nodes was proposed [15]. In the current study, there was no significant association between lymph node status on ultrasonography and SLN positivity; suspicious nodes were positive in 55% and negative in 45% of cases ($P = 0.343$).

Accuracy of SLNB in predicting axillary lymph node status after NAC is currently debatable. Most of the reported experience with SLNB includes patients with clinical stage T1–T2 N0. Locally advanced breast cancer was even considered one of the contraindications. However, recent studies have shown that SLNB can be considered if axillary lymph nodes are negative for metastases even in locally advanced breast cancer [16,17]. The two studies underwent SLNB before NAC and reported that mapping the SLN of these patients with clinically node-negative disease before NAC is accurate, sensitive, and specific.

During their study in locally advanced cases, Cox and colleagues reported on a series of 89 patients with locally advanced breast cancer subjected to SLNB

Table 4 Agreement between Pathology of SLN and non-sentinel nodes

	Pathology of NSLNs		Total
	+ve (*n*=30)	−ve (*n*=22)	
Pathology of SLNs			
+ve			
Count	18	11	29
% within SLNs	62.1%	37.9%	100.0%
% within NSLNs	60.0%	50.0%	55.8%
−ve			
Count	12	11	23
% within SLNs	52.2%	47.8%	100.0%
% within NSLNs	40.0%	50.0%	44.2%

before NAC. Twenty-seven percent of their patients had a complete pathologic axillary response; these patients had a significantly higher overall survival than did patients with residual disease. Their study validated the prognostic stratification of patients with a complete pathological axillary response to NAC [17].

Xing and colleagues in 2006 conducted a meta-analysis of 21 studies (total of 1273 patients) that examined the results of SLNB after chemotherapy. The sensitivity of SLNB in the individual studies ranged from 67 to 100%; the negative predictive value ranged from 56 to 100%; and the overall accuracy ranged from 77 to 100%. The majority of patients in these studies had stage II breast cancer with negative axillary nodes at presentation [18].

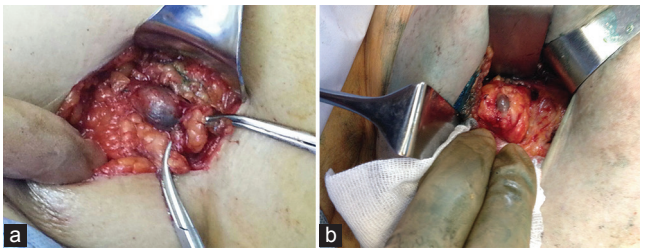
Another systematic review of 27 studies reported a pooled false-negative rate of 10.5% with accuracy of 89.0%. However, authors did not find sufficient evidence to recommend SLNB as a standard procedure after NAC [19].

A more recent meta-analysis reported a 6% false-negative rate and hence concluded that SLNB predicts the pathology of the axilla in patients who are clinically node-negative after NAC with accuracy comparable to that of SLNB for patients with early breast cancer [20].

The high false-negative rate (40%) in the current study precludes the use of SLNB in advanced breast cancer cases. This recommendation was confirmed in previous studies even with lower rates. Ozmen *et al.* [21] reported a 13.7% false-negative rate. Pecha *et al.* [22] concluded that SLNB cannot be recommended as a reliable predictor of axillary lymph node status after NAC. Similarly, Han *et al.* [23] found that general application of SLNB after NAC should be avoided based on a false-negative rate of 10.4%.

The SENTINA study was designed to evaluate optimum timing of SLNB for breast cancer patients treated with NAC. It was a prospective, four-arm multicenter study.

Figure 1



(a, b) Identification of sentinel lymph node.

In this study, arm C was similar to the current study; it involved patients who converted after NAC from N+ to N0. The false-negative rate was 14.2% [24].

In the present study, despite a small sample size, we have shown that SLNB is applicable in locally advanced breast cancer after NAC. Use of patent blue dyes rarely causes complications but has been associated with severe allergic reactions in the literature. Employing two complementary techniques for sentinel node identification will logically improve the sentinel node identification rate and reduce false-negative biopsies (patent blue dye and radioactive colloid) (Fig. 1).

Conclusion

The results of our study support the concept of SLNB feasibility and safety in large primary breast cancer patients who received NAC. Patent blue dye is a safe procedure and none of the patients developed any complications from dye injection. Our accuracy rate, identification rate, and false-negative rate are comparable to reports in the literature on node-negative large primary breast cancer patients after chemotherapy. Consequently, we did not recommend SLNB in these cases as it is unreliable in the prediction of axillary pathology and may lead to an inappropriate management approach.

Lymphatic mapping may not be successful after NAC in large primary breast cancer because of excessive fibrosis of primary tumor and lymphatics and blockage of lymphatic channels with viable or dead materials. Thus we recommend SLNB in clinically node-negative patients before NAC to detect and document axillary nodal disease.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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