Evaluation of the Assessment Tools to Predict Axillary Status Postneoadjuvant Chemotherapy in Locally Advanced Breast Cancer

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ABSTRACT

*This study proposes to replace the completion axillary dissection with the confirmation of a complete pathological response to neoadjuvant chemotherapy among the axillary nodes. That response will be determined by clinical examination, US assessment of axillary lymph nodes (ALNs) and SLNB. From May 2010 to April 2012 we prospectively studied 50 women consecutively selected from among patients presented to Surgical Oncology Department, National Cancer Institute (NCI) who fulfilled the following inclusion criteria: locally advanced operable breast cancer histologically confirmed by thick needle biopsy puncture that had undergone preoperative primary systemic chemotherapy, breast cancer surgery and SLNB with immediate axillary lymphadenectomy. The clinical, sonographic and pathological response of the tumor and the axillary lymph nodes were documented, classified and correlated with each other. The response of the tumor and the axilla were correlated with various patient characteristics and analyzed. Post NACT, on sonographic assessment of the axilla, response was complete in 17 (33.3%) axillae and 34 (66.7%) axillae still showed residual metastatic disease. Complete pathological nodal response (pCR) occurred in 16 (31.4%) axillae and no pathological complete nodal response in 35 (68.9%) axillae. the sentinel lymph node was successfully identified in 39(76.5%) axillae out of 51 axillae; yielding a detection rate of about 76.5% (SLN was not identified in 12 cases. Out of 39 axillae in which SLN were identified there were 32 (82.1%) axillae showed metastatic deposits, while SLN were free of metastatic disease in 7 (17.9%) axillae by hematoxylin and eosin pathological examination. And by using the immunohistochemical examination of negative SLN all of them were also negative with absence of micro metastases, SLN was the only positive node in 9 axillae. Correlation of clinical assessment of ALN versus pathological results (considered as the gold standard) showed that the sensitivity of clinical assessment was 60.0%, specificity was 62.5%, PPV was 77.8%, NPV was 41.7% and accuracy was 60.8%, with p value (0.135). Correlation of US response of ALN versus pathological results (considered as the gold standard) showed that the sensitivity US assessment of ALN was 82.9%, specificity was 68.8%, PPV was 85.3%, NPV was 64.7%, accuracy was 78.5%, with highly significant p value <0.001 . Correlation of SLNB assessment of ALN versus pathological results (considered as the gold standard) showed that Sensitivity of SLNB was 94.1%, specificity was 100.0%, PPV was 100.0%, NPV was 71.4%, accuracy was 94.9% with highly significant p value <0.001. **Conclusion:** We suggest that formal ALND can be avoided post NACT in patients with LABC with cytologically proven metastatic ALN if there were complete clinical, sonographic response and negative SLNB post NACT.*

Key words: *locally advanced Breast Cancer, sentinel Lymph node biopsy.*

INTRODUCTION

The current trend in the management of breast cancer is towards breast conservation whenever possible. With the increasing use of neoadjuvant chemotherapy (NACT), this is becoming a distinct possibility for larger tumors as well. While NACT is the standard treatment for locally advanced breast cancer, recent studies and reviews attempt to address the issue of its use in early operable breast cancer[(1)]. Axillary lymph node dissection (ALND) is still the standard management for axillary nodal metastases[(2)]. Having reached almost a consensus as regards conservation of the breast tissue, surgeons are now taking the conservative approach to the axilla[(3)]. This has been driven by the fact that a considerable amount of treatment related morbidity in breast cancer surgery is related to the axillary evacuation rather than to the resection of the breast tissue itself[(4)]. The role of axillary evacuation is to:

(a) provide accurate prognostic information (b) maintain local control of the disease in the

axilla and (c) provide rational basis for decisions about adjuvant therapy. Although controversial, it may also be associated with a small therapeutic benefit[5]. If a negative axilla can be reliably predicted as negative in the preoperative setting then one can spare the patient an undue axillary evacuation[6]. Several methods have been investigated in this venue, these include sentinel lymph node biopsy (SLNB) and ultrasound (US) guided aspiration[7] .

Given the advances in the efficiency of neoadjuvant chemotherapy in reducing the size of the primary (to the extent of complete gross/ microscopic resolution in some cases), it is logical to assume the same response in the axilla[3]. Many studies have assessed clinical response of axillary nodes to NACT. Some studies have demonstrated complete histopathological response following neoadjuvant chemotherapy. Yet only few have addressed the issue of omission of axillary dissection in a particular subset of patients following NACT[3]. Sentinel lymph node biopsy after NACT is evolving as an alternative to axillary dissection[8,9,10]. There is a reasonable survival rate of breast cancer patients' post neodjuvant chemotherapy and mastectomy that warrants starting looking for avoiding the complications of an undue Axillary dissection. If there is a tool/ tools that can reliably predict the state of the axilla in this subset of patients, then an unnecessary evacuation can be avoided[11].

This study proposes to replace the completion axillary dissection with the confirmation of a complete pathological response to neoadjuvant chemotherapy among the axillary nodes. That response will be determined by clinical examination, US assessment of axillary lymph nodes (ALNs) and SLNB. For this approach to be adopted, 3 things have to be true: (1) the incidence of complete responses must be high enough to make the approach worthwhile; (2) the complete pathological responses have to be real and (3) the incidence of false negative sentinel nodes after neoadjuvant therapy must be low.

MATERIALS & METHODS

Study design

We performed a descriptive study of a series of prospective cases. The clinical, sonographic and pathological response of the tumor and the axillary lymph nodes were documented, classified and correlated with each other. The response of the tumor and the axilla were correlated with various patient characteristics and analyzed. Written informed consent was obtained from all the patients. The study was approved by the Ethical Committee of Clinical Trials of our hospital.

Patients' selection

From May 2010 to April 2012 we prospectively studied 50 women consecutively selected from among patients presented to Surgical Oncology Department, National Cancer Institute (NCI) who fulfilled the following inclusion criteria: locally advanced operable breast cancer histologically confirmed by thick needle biopsy puncture that had undergone preoperative primary systemic chemotherapy, breast cancer surgery and SLNB with immediate axillary lymphadenectomy. We excluded women with inflammatory breast carcinoma, previous breast surgery or axillary or breast radiotherapy, multifocal or multicentric tumors, systemic metastatic disease or second neoplasm, women who were pregnant or in lactation, under 18 years of age, with a history of allergy to human albumin or who withdrew consent at any time during the study. Axillary status was established by physical examination, axillary ultrasonography and ultrasound-guided puncture of the suspicious lymph nodes at both diagnosis and at the end of chemotherapy. For each case, the diagnostic core biopsy was examined for determination of tumor type according to WHO classification[12]. Histological grading was evaluated according to Nottingham combined histologic grade (Elston-Ellis modification of the Scarff Bloom Richardson grading system)[13]. Evaluation of hormonal status; estrogen respecters (ER) & progesterone receptors (PR) according to Allred scoring system[14]. HER2/neu immunostaing results were estimated according to HER2/neu scoring system used to evaluate Hercep Test[15].

Response to NACTH:

Neoadjuvant chemotherapy was given for a median of 4 cycles (range from 3 to 6 cycles). The patients received the NCI standard of care chemotherapy regimens that was FEC in 41 patient (FEC 100 in 30 patients &FEC 57 in 11 patients) & FAC in 9 patients, with treatment dosage as follows: F (5 Fluorouracil) dose 500mg /m2 , E (Epirubicin) dose 100mg/m2, A (Doxorubicin) dose50mg/m2 , C (Cyclophosphamide) dose 500mg/m2

The clinical, sonographic response of the tumor and the axillary lymph nodes were documented and classified as per the WHO criteria (16) as: complete response (cCR), partial response (cPR) or no response (cNR). We defined complete sonographic response of the axilla (negative axilla by ultrasound) as the absence of

any detectable sonographic criteria of metastatic deposit in axillary lymph nodes including: longitudinal to transverse axis ratio of less than 2 imparting a rounded appearance to the lymph node, poor central hilum, absence of a fatty hilum and eccentricity of the nodal cortex together with nodal size greater than 20 mm[17], concentric or eccentric thickening of the cortex to more than 2 mm, focal doubling of the cortical thickness [18,19].

Sentinel Lymph Node Biopsy:

Sentinel lymph node (SLN) identification was performed using patent blue dye injection. The patient is prepped and draped in the operating room, injection sites were superficial around the tumor (peritumoral), subareolar or periareolar, left to the discretion of the participating surgeons, 2-3 mL of patent blue was injected under general anesthesia after injection breast massage was performed for 10 minute. Axillary fascia is entered through a formal transverse axillary incision and blunt dissection was performed until a blue-stained lymphatic tract or node was visualized. The blue lymphatic vessel was dissected into the axilla until the first lymph node was encountered. All blue LNs and any LNs at the end of a blue lymphatic channel are removed and designated as SLNs. After excision of sentinel lymph nodes, all patients underwent a level I to II axillary lymphadenectomy, followed by the appropriate mastectomy procedure as dictated by each patient's condition individually. The whole sentinel lymph nodes were submitted and labeled separately from the rest of the axillary lymphadenectomy.

Pathologic Analysis:

Haematoxylin and eosin slides of each case were prepared from each formalin fixed paraffin block for proper evaluation of pathologic response of tumor as well as lymph nodes, together with routine histpathologic examination for evaluation of surgical margins and extent of tumor involvement. Additional one positively charged slide was prepared from each case with microscopically proved negative sentinel node/s for staining with pan cytokeratin (Dako, mouse monoclonal antibody, clone AE1/AE3, ready to use)

Pathological response in the surgically resected specimen was based on exhaustive microscopic examination of multiple sections from the breast and axillary lymph nodes according to: Primary tumor was evaluated according to Miller and Payne scoring system[20], lymph node status was evaluated according to National Surgical Adjuvant Breast and Bowel Project scoring system[21]. Complete pathological response (pCR): was defined as grade 5 according to Miller, Payne. Partial pathological response: was defined as grades 3 and 4 according to Miller, Payne. The clinical, songraphic and pathological response of the tumor and the axillary lymph nodes were documented, classified and correlated with each other. The response of the tumor and the axilla were correlated with various patient characteristics and analyzed.

RESULTS

In the current study, fifty patients were enrolled one of them had bilateral breast cancer so there were 51 tumors.Patient's mean age was 47.7±9.1 years; twenty eight (56%) patients were postmenopausal. Tumor was in right side of the breast in 29 (58%) patients, and only one female patient (2%) had bilateral breast cancer. The mean clinical tumor size was 6.7±1.4cm; the commonest TNM stage initially was stage IIIA that was presented in 32(62.7%) tumors. The initial mammographic finding of the tumors (BIRADS SCORE) was mainly BIRADS score (V) in 42 (82.4%) tumors and all axillary lymph node showed malignant criteria with axillary US assessment before starting chemotherapy. The commonest histological subtype of breast cancer encountered initially was invasive duct carcinoma(IDC) in 46 (90.2%) tumors , the grade was mainly of grade II in 46 (90.2%) tumors, and regarding receptors status; ER was positive in 25(49%) tumors, PR was positive in 28(54.9%) tumors and HER2/neu was (+3) only in 4(7.8%) tumors. (Table1)

Table (1): Patients, tumor and pathological characteristics, initial radiological assessment of the breast tumors & axillary lymph nodes

Characteristic	Number (%)	Initial Mammogram (BI-RADS Score)	Number (%)
Total number	50(100)	◎ IV	4 (7.8)
Age		◎ V	42 (82.4)
Mean ±SD	47.7±9.1	◎ VI	5 (9.8)
Median (range)	48 (24-66)	**Axillary US**	
Menopausal status		Non-malignant LNs	0
Postmenopausal	28 (56)	Malignant LNs	51 (100.0)
Premenopausal	22 (44)	**Histologic subtypes**	**Number (%)**
Laterality		Total	51
Right	29 (58)	IDC	46 (90.2)
Left	20 (40)	ILC	4 (7.8)
Bilateral	1 (2)	Unclassified carcinoma	1 (2)
Tumor size		**Grade**	
Mean ±SD	6.7±1.4	◎ Grade I	3 (5.9)
Median (range)	6 (5-12)	◎ Grade II	46 (90.2)
T stage		◎ Grade III	2 (3.9)
◎ T0	0	ER receptor status	
◎ T1	0	Negative	26 (51)
◎ T2	0	Positive	25 (49)
◎ T3	32 (62.7)	PR receptor status	
◎ T4	19 (37.3)	Negative	23 (45.1)
N stage		Positive	28 (54.9)
◎ N0	0	HER2/neu	
◎ N1	48 (94.1)	◎ 0	32 (62.7)
◎ N2	3 (5.9)	◎ 1	12 (23.5)
TNM stage		◎ 2	3 (5.9)
◎ IIIA	32 (62.7)	◎ 3	4 (7.8)
◎ IIIB	19 (37.3)		

SD: standard deviation, TNM: tumor, node, metastases. BI-RADS: breast imaging reporting and data system, US: ultrasound, LN: lymph node. IDC: invasive duct carcinoma, ILC: invasive lobular carcinoma, ER: estrogen, PR: progesterone, HER2/neu: human epidermal growth factor receptor 2

Assessment of breast tumor response to NACT

Following NACT, there was reduction of the mean clinical tumor size from 6.7 ±1.4 cm to 4.3 ± 2.7 cm with significant p value <0.001. Clinical response was complete response (ycCR) in 4 (7.8%) tumors, partial response (ycPR) in 23 (45.1%) tumors and stationary disease in 24 (47.1%) tumors and there were no patient showed progressive disease under NACT. Clinically the breast tumor diameter was ranging from 2 to 5 cm (T2) in 19 (37.3) tumors and (yTNM) stage was mainly (yIIB) in 15 (29.4%). Following NACT, there was pathological primary tumor response in 40 (77.4%) tumors ranging from mild therapeutic response in 20 (39.2%) tumors to complete therapeutic response (pCR) in 8 (15.7%) tumors**.** There were no major variation between histological subtypes or grade assessment preoperatively & post operatively (p>0.05). One tumor that was preoperatively diagnosed as ILC, diagnosed postoperatively as IDC. Two tumors were diagnosed preoperatively as grade II but postoperatively as grade III.

Assessment of axillary nodal response to NACT

Post NACT there was complete clinical nodal response (ycN0) in 24 (47.1%) axillae, twenty sex

(51%) axillae had clinically mobile ipsilateral metastatic axillary lymph node (ycN1) and only one axilla (2%) had matted ipsilateral axillary lymph node (yN2) **.**On sonographic assessment of the axilla, response was complete in 17 (33.3%) axillae and 34 (66.7%) axillae still showed residual metastatic disease**.** Complete pathological nodal response (pCR) occurred in 16 (31.4%) axillae and no pathological complete nodal response in 35 (68.9%) axillae, with capsular rupture in 27(77.1%) axillae out of 35 axillae with positive axillary lymph metastases**.** ***(Table 2)***

Table (2): Clinical, radiological, pathological response of axillae to NACT

Post NACT N stage	**Number (%)**	**Pathological nodal response**	
Total	51	**No pCR**	35 (68.9)
◎ N0	24 (47.1%)	**pCR**	16 (31.4)
◎ N1	26 (51%)	**Capsular rupture (positive axillae)**	
◎ N2	1 (2%)	**Total**	35
Post NACT axillary US		Positive	27 (77.1)
Non- malignant LN	17 (33.3)	negative	8 (22.9)
Malignant LN	34 (66.7)		

NACT: neoadjuvant chemotherapy, US: ultrasound,
N: lymph node, PCR: pathological complete response

Sentinel lymph node (SLN) and Non-SLN

Using patent blue dye injection method only, the sentinel lymph node was successfully identified in 39(76.5%) axillae out of 51 axillae; yielding a detection rate of about 76.5% (SLN was not identified in 12 cases. At least one sentinel lymph node was successfully identified and harvested for histological evaluation. Mean number of sentinel lymph nodes harvested per patient was 3.1± 1.1.Three lymph node were identified in 13(33.3%) axillae and four sentinel lymph node were identified in 13(33.3%) axillae. Out of 39 axillae in which SLN were identified there were 32 (82.1%) axillae showed metastatic deposits, while SLN were free of metastatic disease in 7 (17.9%) axillae by hematoxylin and eosin pathological examination. And by using the immunohistochemical examination of negative SLN all of them were also negative with absence of micro metastases, SLN was the only positive node in 9 axillae. ***(Table3)*** The mean number of the total dissected ALN was 18 ± 5.7 and the mean number of non-sentinel lymph nodes were 15.4 ±5.6. Non SLN were positive in 26(51%) axillae and negative in 25 (49%) axillae. ***(Table3)***

Table (3): Detection rate, number and status of SLN

Identification of SLN	**Number (%)**	**SLN status by IHC**	**Number(%)**
Total	51	Total	7
◎ Identified	39 (76.5)	◎ Positive	0
◎ Unidentified	12 (23.5)	◎ Negative	7 (100)
Number of SLN	**Number (%)**	**Number of total Positive ALN**	**Number(%)**
Total	39	◎ Mean ±SD	4.5±5.3
◎ 1	1 (2.6)	◎ Median (range)	2 (0-22)
◎ 2	11 (28.2)	Number of Non-SLN	
◎ 3	13 (33.3)	◎ Mean ±SD	15.4±5.6
◎ 4	13 (33.3)	◎ Median (range)	15 (7-32)
◎ 7	1 (2.6)	**Non-SLN status**	**Number (%)**
◎ Mean ±SD	3.1±1.1	◎ Positive	26 (51)
◎ Median (range)	3 (1-7)	◎ Negative	25 (49)
SLN status by HE	**Number (%)**		
Total	39		
◎ Positive	32 (82.1)		
◎ Negative	7 (17.9)		

SLN: sentinel lymph node, SD: standard deviation, HE: hematoxylin and eosin, IHC: immunohistochemistry

The false-negative rate was defined as the ratio of the number of axillae with a false-negative case of SLNB (2 axillae) to the number of axillae with at least one involved node (> 2 mm), SLN or not, (34 axillae) among patients with at least one detected SLN. So the false negative rate in the current study was 5.8% ***(table4)***

Table (4): Correlation between SLN and non SLN status

		SLN status		*Total*	*P value*
		Positive	*Negative*		
Non SLN status	*Positive*	*23 (92.0%)*	*2 (8.0%)*	*25 (100.0%)*	*0.075*
	Negative	*9 (64.3%)*	*5 (35.7%)*	*14 (100%)*	
Total		*32*	*7*	*39*	

SLN: sentinel lymph node

Correlation of clinical and sonographic response of ALN to pathological response (Table 5)

Out of 24 axillae that showed clinical complete nodal response only 10 axillae showed complete pathological nodal response. Correlation of clinical assessment of ALN versus pathological results (considered as the gold standard) showed that the sensitivity of clinical assessment was 60.0%, specificity was 62.5%, PPV was 77.8%, NPV was 41.7% and accuracy was 60.8**%,** with p value (0.135). Out of 17 axillae that showed complete sonographic response 11 axillae showed complete pathological nodal response and 6 cases

showed no complete pathological response. Correlation of US response of ALN versus pathological results (considered as the gold standard) showed that the sensitivity US assessment of ALN was 82.9%, specificity was 68.8%, PPV was 85.3%, NPV was 64.7%, accuracy was 78.5%, with highly significant p value **<0.001**

Correlation of SLN status and identification to pathological nodal response

Two axillae out of seven axillae with negative SLN showed residual disease and all axillae with positive SLN had residual disease. Correlation of SLNB assessment of ALN versus pathological results (considered as the gold standard) showed that Sensitivity of SLNB was 94.1%, specificity was 100.0%, PPV was 100.0%, NPV was 71.4%, accuracy was 94.9% with highly significant p value **<0.001**

Eleven axillae out of the unidentified 12 axillae were in a complete pathological nodal response. Sensitivity was 97.1%, specificity was 68.8%, PPV was 87.2%, NPV was 91.7%, and accuracy was 88.3%, p value<0.001.

Correlation between pathological nodal response to pathological tumor response and NACT regimen

Out of 16 axillae that showed complete pathological nodal response 7 breast tumors showed complete tumor response .In the current study there were pCNR in 14 out 41 axillae that received FEC, and pCNR in 2 out of 9 axillae that received FAC.

Table (5): Correlation of Pathological nodal response with other factors

		PNR		Total	P value
		NO PCR	PCR		
Post_NACT_clinical N response	N+ (no cCR)	21 (77.8%)	6 (22.2%)	27 (100%)	0.135
	N0 (cCR)	14 (58.3%)	10 (41.7%)	24 (100%)	
Total		35	16	51	
		PNR		Total	P value
		NO CR	CR		
Post NACT axillary US	Malignant LNs (no CR)	29 (85.3%)	5 (14.7%)	34 (100%)	< 0.001
	Non-malignant LNs (CR)	6 (35.3%)	11 (64.7%)	17 (100%)	
Total		35	16	51	
		PNR		Total	P value
		NO CR	CR		
SLN status	Positive (noCR)	32 (100%)	0 (0%)	32 (100%)	< 0.001
	Negative (CR)	2 (28.6%)	5 (71.4%)	7 (100%)	
Total		34	5	39	
		PNR		Total	P value
		NO CR	CR		<0.001
Identification of SLN	Identified	34 (87.2%)	5 (12.8) %)	39 (100%	
	Unidentified	1 (8.3%)	11 (91.7%)	12 (100.0%)	
Total		35	16	51	
		NACT Regimen		Total	P value
		FEC	FAC		
PNR	No CR	27	7	34	0.699
	CR	14	2	16	
Total		41	9	50	

PNR: pathological nodal response, NACT: neo adjuvant chemotherapy, N: lymph node, cCR: complete clinical response, LN: lymph nodes, US: ultrasound SLN: sentinel lymph node

DISCUSSION

Our series is a prospective series designed to address these questions; is the incidence of complete pathological nodal response (axillary conversion) is high enough to make the conservation of axilla post NACT worthwhile? Is the pathological response a real response? Is there are any tools that could accurately predict ALN status post NACT? Is SLNB feasible and accurate after NACT for large operable breast cancer?

Present study documented complete axillary conversion from cytologically positive LNs into negative in 31.4% of patients following NACT. Pathological complete response of cytologically positive axillary LNs following NACT was documented in various studies varying from 23% up to 36% [22,23]. Other studies have reported conversion of clinically involved axilla to a pathologically negative status in 25% to 38% of patients following NACT. The nodal metastasis was not cytologically documented before administering chemotherapy in these studies [23,24].

Documentation of metastasis in axillary nodes before initiation of chemotherapy, as done in present study, is essential to demonstrate complete pathological response following NACT. Clinically palpable nodes cannot be assumed to be metastatic all the times. In current study, we observed that six patients who had clinically palpable nodes did not have metastasis.

In the current study, there was complete pathological nodal response (pCR) in 14 out 41 axillae (34.1%) that received FEC and pCR in 2 out of 9 axillae (22.2%) that received FAC. The higher pCR with FEC can be explained by the higher dose of the Epirubicn compared to doxorubicin (75 or 100 mg vs. 50 mg).

Pathological response rate is improved with induction of other effective chemotherapy regimens, including taxanes [25,26]. Taxanes added either concurrently or in sequence to anthracycline-based regimens and showed increased response rates in the neoadjuvant setting[27]. Recently Trastuzumab was added to various NACT regimens in several phase II trials, Large phase III resulted in pCR rates ranging from 12% to 76% percent[28,29]. The addition of gemcitabine or capecitabine to anthracycline- and taxane-based regimens is under investigation [30].

NACT in current study was given for a median of 4 cycles. Then they were evaluated clinically for response. The mean number of CTH cycles was 4.1± 1**.** The optimal duration of NACT has not been established. More prolonged duration, typically six rather than three or four cycles of NACT has generally resulted in higher pathologic complete response (pCR) rates [31]. Expert recommendations are to administer four to six cycles of NACT, as long as there is no disease progression[32]. Although the optimal timing is unknown, some prefer completing the course of chemotherapy before surgery rather than dividing it between the preoperative and postoperative setting, in order to increase the chance of pCR and breast conservation [32].

Preoperative axillary staging in the earlier randomized NACT trials was achieved by physical examination. Before the introduction of neoadjuvant therapy, a number of authors examined the accuracy of clinical axillary examination relative to the final pathology**.** The positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of physical examination ranged from 65% to 82%, 50% to 61%, and 61% to 68%, respectively, demonstrating that axillary staging by physical examination alone is unreliable [33]. In our study, the PPV, NPV, and accuracy were 77.8%, 41.7% and 60.8%, respectively (p 0.135).

The use of ultrasound (US) to detect metastases in lymph nodes was examined [34], also the ability of high-resolution axillary US to predict pathologic lymph node status specifically in patients with locally advanced breast tumors undergoing NACT was studied; the PPV of post chemotherapy axillary US compared to physical examination was 83% vs. 93%, and the NPV was 52% vs. to 58% [35,7].

In the current study, considering pathological results of ALND as the gold standard, ultrasonography was found to be better than clinical examination in the assessment of axillary nodes and their response to NACT with sensitivity 82.9% vs. 60%; specificity 68.8% vs. 62.5% PPV 85.3% vs. 77.8% NPV 64.7% vs. 41.7% and accuracy rate was 78.5% vs. 60.8% respectively ($p < 0.001$).

Other studies comparing clinical examination, sonography and mammography concluded that sonography was the best single non-invasive method of assessing the extent of nodal involvement[36,37,38]. The sensitivity and specificity of ultrasonography for detection of axillary lymph nodes have been reported to range from 56% to 73% and 70% to 90%, respectively[36].

In our study the high sensitivity of axillary sonography could be attributed to using a lot of

sonographic criteria of metastatic deposits and the definition of complete sonographic response as the absence of any detectable sonographic criteria of metastatic deposit in axillary lymph nodes that were mentioned earlier.

Some studied examined the accuracy of US-guided fine-needle aspiration (FNA) for indeterminate and suspicious axillary lymph nodes in the initial staging of breast cancer. They found that the sensitivity of US-guided FNA was highly dependent on the size of the metastatic deposit. When the metastatic deposit was <0.25 mm, the sensitivity was 16%; if the metastasis was >1.5 cm, the sensitivity increased to 88%[39,40]. On the basis of these studies, US with FNA cytology are better than US alone and physical examination in evaluating the axilla. The specificity is high, and false-positive cases are rare. Furthermore, although a cytologically positive lymph node accurately determines axillary lymph node status, a cytologically negative lymph node does not.

The use of other imaging modalities in the preoperative staging of the axilla has been explored. Preoperative magnetic resonance imaging (MRI) of the axilla was performed, and axillary lymph node metastases were identified with a sensitivity, specificity, and accuracy of 83%, 90%, and 88%, respectively[41].

Combination of bilateral breast MRI and high-resolution MRI of the axilla was investigated. This enabled one MRI of the breast and axilla to be performed rather than performing a separate MRI of the axilla. The most important features suggestive of malignancy included the presence of nodes with irregular borders, high signal intensity on T2-weighted images, marked gadolinium enhancement, and round hila with abnormal cortices. On the basis of these criteria, the false-positive rate was 12% and the false-negative (FN) rate was 13% [42].

Other study compared preoperative non-contrast MRI to MRI by means of a lymph node–specific magnetic resonance contrast agent known as ultra-small super paramagnetic iron oxide (USPIO). Non-contrast MRI yielded sensitivity, specificity and accuracy of 71%, 84%, and 79%, respectively; the use of USPIO-enhanced MRI increased those values to 100%, 98%, and 98%, respectively. This technique is variable among institutions, and it is not easily accessible or cost-effective [43].

Several studies examined Using 2-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan in predicted axillary node status; the sensitivity, specificity, PPV, and NPV were 61%, 80%, 62%, and 79%, respectively. They also found that the accuracy for detecting axillary metastases was improved with the presence of multiple positive lesions, intense lesions, smaller size of the patient, and larger size of the tumor. They concluded that FDGPET is currently not a suitable substitute for ALND in the assessment of axillary lymph nodes in breast cancer patients[44,45].

So, there are a number of imaging modalities that can detect axillary metastases with variable accuracy rates. All imaging modalities are limited by the inability to detect small metastases, resulting in high FN rates. False-positive results can be eliminated by the use of image-guided needle biopsy. However, there is currently no imaging modality that can replace surgical staging of the axilla.

Giving the possibility of missing a positive axilla either by clinical examination or radiological (ultrasonography) assessment of axilla; another modality/technique was invited in current study for better assessment and more accurate prediction of ALN status post NACT.

It is currently debatable whether SLNB can accurately predict axillary lymph nodes status after NACT, the hypothesis 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 [46, 47].

To avoid difficulties resulting from pathologic modifications of the lymphatic pathway secondary 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[36,48,49]. This strategy has two main disadvantages: first, each woman with involved SLNs will experience two separate axillary surgical procedures, before and after NAC, and second, women with lymph node metastasis at presentation, eradicated by NAC, will undergo an unnecessary lymphadenectomy[36,50]. SLNB performed after NAC eliminates the need for two axillary surgical procedures for patients with involved sentinel nodes allows pathologic evaluation, and may avoid a systematic axillary lymphadenectomy in the case of lymph node down staging.

Several series, have been published dealing with SNLB after NACT, Apart from few series with more than 100 patients, the average rate of

inclusions was 37 patients. These series are mainly retrospective, and only few series were multi-institutional [23,46,51,52,53,54].

When only the four largest series of 100 patients or more are considered, the results reported detection rates ranging from 85% to 93% and false-negative rates ranging from 8% to 10.7%[23,46,52,53]. These results are comparable to the detection rate and false-negative rate of SLNB in the case of early breast cancer pooled in a recent meta-analysis [55].

According to data from the American College of Surgeons Oncology Group (ACOSOG) Z1071 study, NACT resulted in eradication of lymph node disease in 40% of node positive locally advanced breast cancer patients. SLN surgery after NACT in node positive breast cancer patients correctly identified nodal status in 84% of all patients and was associated with a FNR of 12.8%, therefore could provide a less invasive option than axillary lymph node dissection for nodal staging in this population[56].

Current study showed that SLN detection rate using single method (patent blue dye injection) was 76.5%, considering the pathological result of ALND as the gold standard, the sensitivity of SLNB in predicting ALNs response after NACT was 94.1%, specificity was 100.0%, PPV was 100.0%, NPV was 71.4%, a false negative rate of 5.8%, accuracy was 94.9% with highly significant p value <0.001. The detection rate in this study was 76.5%, some of the reported series have detection rate up to 100%. The pooled results of detection rates published in a recent meta-analysis of SLNB after NAC, ranging from 72% to 100%[46,57]. We attributed the relatively low rate of detection in the current study to the fact that only one technique was used, namely patent blue dye injection.

The methods of SLN detection have an impact on both the detection rate and the false-negative rate[52,55]. In our prospective series, we used only one method, in other study the detection rate was 87.6% with the combined methods and 78.1% with blue dye alone [52]. Boughy and her colleagues concluded that false-negative rate is lower with use of dual tracer (blue dye and radiolabelled colloid) and the more SLNs are removed. Therefore, technical factors are important to minimize incorrect nodal staging [56].

False-negative rate assessment requires both an SLNB and a complete level I to II lymphadenectomy[46]. In the current study the false-negative rate was 5.8% while in recent meta-analysis of SLNB after NACT it was 12% and 9.8% in results of National Surgical Adjuvant Breast and Bowel Project B32 trial [57,58] and this low figure of false negative rate in our study may be attributed to small patient number. Only three series have revealed a false-negative rate of up to 20%, with a small cohort, and in two, a low detection rate less than 90% was also noted[59,60,61].

To reduce the SLNB false-negative rate after NAC, some proposed an axillary intraoperative ultrasound assessment after SLNB to explore the non-sentinel region for additional suspicious lymph nodes, reducing the false-negative rate from 9.6% to 1.39%[62]. In the case of patients treated for an early breast cancer, a positive preoperative positron emission tomography imaging showing suspicious axillary lymph nodes may indicate a lymphadenectomy rather than a SLNB, with a high specificity limiting the false-negative rate [63].

The impact of pretherapy axillary lymph node assessment on false-negative rate remains controversial. The false-negative rate from the National Surgical Adjuvant Breast and Bowel Project B-27 trial did not differ for patients with clinical N0 disease as compared with those with clinical N1 disease[52]. In a study of patients with SLNB and axillary lymphadenectomy with suspicious axillary lymph nodes, there was no difference in false-negative rate and accuracy when comparing the group of patients treated with NAC to the group of patients treated without NAC [64]

The correlation between the false-negative rate and the pathologic response to treatment is rarely studied. In a series of patients with pretreatment biopsy-proven axillary metastasis, they demonstrate a high SLNB accuracy after a complete or partial pathologic response to NAC [54]. The high false-negative rate observed with a series of patients with pretreatment biopsy-proven axillary metastasis may be linked to the lack of immunohistochemical analysis. An examination of SLNs by serial sectioning and immunohistochemical staining significantly increases the detection rate of micrometastasis, which could reduce the rate of false-negative cases [61]. In the current study all negative SLN by H&E were subjected to IHC pathological examination none of them showed micrometastatic disease.

CONCLUSION

Present study documented complete pathological axillary conversion (confirmed by meticulous pathological examination using H&E

and IHC) in 31.4% of patients following NACT which is a high percentage regarding pathological response of breast tumor that can be improved with marvelous advances in NACT making trial of conservation of axilla post NACT worthwhile. Axillary predictors studied in present study showed collectively high sensitivity and specificity in accurately predicting axillary status post NACT with low false negative rate.

The detection and false-negative rates of SLNB did not differ from those obtained in the case of early breast cancer without NAC, thus demonstrating the feasibility and accuracy of SLNB after NAC. We suggest that formal ALND can be avoided post NACT in patients with LABC with cytologically proven metastatic ALN if there were complete clinical, sonographic response and negative SLNB post NACT.

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