The Accuracy of Sentinel Lymph Node Biopsy Following Neoadjuvant Chemotherapy in Clinically Node Positive Breast Cancer Patients: A Single Institution Experience

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Abstract

Background: Sentinel lymph node dissection after neoadjuvant chemotherapy is of questionable accuracy.
Objectives: In this study, accuracy and feasibility of sentinel lymph node biopsy in patients with breast cancer presented with clinically positive axillary nodes were evaluated.
Methods: We conducted a cross sectional study on patients with breast cancer treated at Milad Hospital of Tehran, Iran from June 2014 to February 2015. Clinically node positive patients (proven by biopsy), who became clinically node-negative by ultrasonography and physical examination following neoadjuvant chemotherapy and had been dissected up to 3 lymph nodes according to sentinel lymph node pattern, were included in the study. We used a 2×2 contingency table to analyze the feasibility of sentinel lymph node biopsy (sensitivity, specificity, false negative ratio, and accuracy). STATA statistical software (version 13.0, StataCorp LP, Texas, USA) was used for statistical analysis.
Results: Among 52 patients, who entered the study, 47 patients had been dissected up to 3 lymph nodes according to sentinel lymph node pattern. We achieved a sensitivity of 100% (16/16), false-negative rate of 0% (0/21), a negative predictive value of 100% (26/26), and an overall accuracy of 89.4%.
Conclusions: Sentinel lymph node dissection seems to be feasible and accurate in clinically lymph node positive patients with breast cancer, who achieve a clinically negative node status by ultrasonography and physical examination, following neoadjuvant chemotherapy.

Keywords: Breast Neoplasms, Neoadjuvant Therapy, Sentinel Lymph Node Biopsy

1. Background

In recent years, axillary lymph node dissection (ALND) has been largely replaced by sentinel lymph node biopsy (SLNB) as the standard technique for axillary staging in patients with early stage breast cancer. This is because many trials have shown that SLNB has comparable accuracy with ALND, while causing lower rates of morbidity (1).

In women with T1 - T2 breast cancer and clinically negative axillary nodes by ultrasonography and physical examination, SLNB is able to identify more than 90% of positive nodes, with a false-negative rate of less than 10% (2).

Nowadays, many patients with locally advanced breast cancer (especially individuals with positive axillary lymph nodes) are planned to receive neoadjuvant chemotherapy (NAC) before surgery (3).

However, there is a large debate over the role of SLNB in patients, who have received NAC. Although small institutional studies have reported different false negative rates (FNRs) for SLNB after NAC, a recent meta-analysis has shown that SLNB can be considered as an accurate and reliable tool in order to make treatment decisions for patients, who have received NAC (4).

As the majority of the published papers have included both clinically positive and negative axillary nodes (by ultrasonography and physical examination) in their studies, FNRs of the SLNB following NAC might have been underestimated (5).

Some trials, however, have exclusively enrolled clinically node positive patients in their studies, which has resulted in higher false negative rates (6-10).

In this study, accuracy and feasibility of sentinel lymph node biopsy in patients with breast cancer presented with clinically positive axillary nodes were evaluated.

2. Methods

2.1. Study Design

We conducted a cross sectional study on patients with breast cancer treated at Milad Hospital of Tehran, Iran from June 2014 to February 2015.

Clinically node positive patients (proven by biopsy), who became clinically node-negative by ultrasonography and physical examination following neoadjuvant chemotherapy and had been dissected up to 3 lymph nodes according to sentinel lymph node pattern, were included in the study.

Exclusion criteria were as follow: inflammatory breast cancer, metastatic disease, and patients with clinically positive axillary nodes after NAC. Furthermore, patients whose sentinel nodes could not be identified were excluded.

Tumor staging was done based on the TMN staging system. All patients underwent complete ALND after SLNB.

All patients signed the consent form, and the study was approved by the research Ethics Committee of Milad Hospital.

2.2. Sentinel Lymph Node Biopsy

We used Technetium-99 for axillary lymph node mapping. To do so, 0.4 mL 30 MBq (0.5 - 0.8 mCi) 99mTc tin colloid was injected in day of surgery at 3 to 4 sub-areolar and sub-dermal areas. SLNs were determined, using Gamma probe in the operating theatre.

The node showing the highest radioactivity as well as all radioactive nodes with a count $\geq$ 10% of the highest radioactive node were removed and sent for frozen section diagnosis.

2.3. Statistical Analysis

We used a 2 × 2 contingency table to analyze the feasibility of SLNB (sensitivity, specificity, false negative ratio, and accuracy). STATA statistical software (version 13.0, StataCorp LP, Texas, USA) was used for statistical analysis.

2.3.1. False Positive (FP)

Patients with positive SLN, but negative ALN.

2.3.2. False Negative (FN)

Patients with negative SLN, but positive ALN.

2.3.3. True Negative (TN)

Patients with negative SLN and ALN.

2.3.4. True Positive (TP)

Patients with positive SLN and ALN.

2.3.5. Sensitivity

Number of patients, who had positive SLN and ALN per number of patients who had negative SLN but positive ALN plus number of positive SLN and ALN patient (TP/[FN + TP]).

2.3.6. Specificity

Number of patients with negative SLN and ALN per patient, who had positive SLN and negative ALN plus patients with negative SLN and ALN (TN/[FP + TN]).

2.3.7. Negative Predictive Value (NPV)

Number of patients with negative SLN and ALN per patients with negative SLN and positive ALN plus patients with negative SLN and ALN (TN/[FN + TN]).

2.3.8. Positive Predictive Value (PPV)

Number of patients with positive SLN and ALN per patient, who had positive SLN and negative ALN plus patients with positive SLN and ALN (TP/[FP + TP]).

3. Results

Among 52 patients, who entered the study, 47 patients had been dissected up to 3 lymph nodes according to sentinel lymph node pattern. Their characteristics are shown in Table 1.

Following neoadjuvant chemotherapy, pathologic complete response (PCR) was observed in 8 patients (17.0%) (Table 2).

In this study, positive sentinel lymph nodes are in 21 patients and negative sentinel lymph nodes are in 26 patients.

In all 26 patients with negative sentinel lymph node, the results of pathologic examination of axillary lymph node dissection also showed no lymph node involvement.

In 16 out of 21 patients, who had a positive result in frozen examination of sentinel lymph node, the pathological evaluation of non-sentinel nodes were also positive. In 5 patients with positive sentinel nodes, the pathological examination of non-sentinel nodes were negative and did not involve metastasis (Table 3).

We achieved a sensitivity of 100% (16/16), false-negative rate of 0% (0/21), a negative predictive value of 100% (26/26), and an overall accuracy of 89.4% (42/47) (Table 4 and Figure 1).

Table 1. Clinical Characteristics of the Patients

Variables	Number	Frequency, %
Age		
50 - 60	20	42.6
60 - 70	27	57.4
Estrogen receptors		
Positive	26	55.4
Negative	19	40.4
Missing	2	4.2
Progesterone receptors		
Positive	21	44.8
Negative	24	51.0
Missing	2	4.2
Her2 Status		
Positive	31	65.9
Negative	14	29.9
Missing	2	4.2
Lymph node dissection		
ALND		
Positive	16	34.0
Negative	31	66.0
SLND		
Positive	21	44.7
Negative	26	55.3
Pathologic complete response		
Yes	8	17.0
No	39	83.0

Table 2. TNM Staging of the Patients Before NAC and After NAC and Surgery

Variables	Number of Subjects Clinical Staged Before NAC	Number of Subjects Pathological Staged After NAC and Surgery	P Value
T-stage			0.0001
T 0	0	9 (19.2)	
T 1	0	19 (40.4)	
T 2	0	15 (31.9)	
T 3	22 (46.9)	4 (8.5)	
T 4	25 (53.1)	0	
N-stage			0.0001
N 0	0 (0)	27 (57.4)	
N 1	23 (49.0)	16 (34.0)	
N 2	24 (51.0)	4 (8.5)	
N 3	0	0	
Overall stage			0.0001
0	0	8 (17.0)	
I	0	13 (27.6)	
IIA	0	12 (25.5)	
IIB	0	10 (21.2)	
IIIA	23 (47.9)	4 (8.5)	
IIIB	24 (52.1)	0	
IV	0	0	

Abbreviation: NAC, neoadjuvant chemotherapy.

Table 3. Positive and Negative Sentinel Lymph Nodes After Neoadjuvant Chemotherapy When Sentinel Nodes Were Successfully Identified (n = 47)

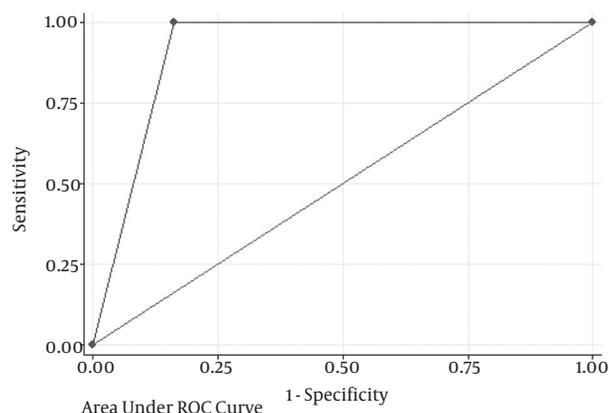|	Non-Sentinel Node with Metastasis	Non-Sentinel Node Without Metastasis	Total
Positive sentinel lymph nodes	16	5	21
Negative sentinel lymph nodes	0	26	26

Figure 1. ROC analysis of SLNB as a diagnostic test VS ALND after neoadjuvant therapy in patients with breast cancer

4. Discussion

Feasibility and accuracy of SLNB after preoperative NAC is controversial ([11]). A recent meta-analysis suggested that SLNB can be used as a feasible test in node-negative patients ([4]). Furthermore, large clinical trials and multicenter studies in clinically node negative (by ultrasonography and physical examination) patients have reported similar false negative rates for SLNB before and after NAC ([9, 10]).

The value of SLNB after NAC is more of a question in clinically node-positive diseases, and some experts consider it contraindicated in these patients. This inaccuracy has several possible reasons. Neoadjuvant chemotherapy

Table 4. Diagnostic Evaluation of SLNB After Neoadjuvant Therapy When Pathologic Evaluation of ALND Assumed as a Gold Standard

	Value	95% CI
Median number of removed lymph nodes (range)	3 (3 - 7)	
Sensitivity	100% (16/16)	79.4 - 100
Specificity	83.8% (26/31)	66.3 - 94.5
Negative predictive value	100% (26/26)	86.7 - 100
Positive predicative value	76.2% (16/21)	52.8 - 91.8
False positive rate	16% (5/31)	35.9 - 7.22
False negative rate	0	0
Accuracy (area under ROC curve)	89.4%	76.9 - 97.6

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

may cause lymphatic fibrosis and hence, alterations in the lymphatic drainage pattern. Furthermore, it is possible that chemotherapy affects the nodes in a non-sequential pattern, and sentinel nodes might be negative before non-sentinel nodes.

The findings of this study showed acceptable accuracy and false negative rate of SLNB, as no false negative case (negative in SLNB and positive in ALND) was observed.

Sensitivity, specificity, accuracy, and false negative rates were reported as 100%, 83.8%, 89.4%, and 0%, respectively.

According to the previous studies, false negative rates for SLNB after neoadjuvant chemotherapy in cN0 patients vary from 0% to 20%. For patients with clinically positive nodes, this figure can be as high as 30% (4, 11).

Two large clinical trials have evaluated the accuracy of SNLB after NAC in clinically node-positive patients: ACOSOG Z1071 (9) and SENTINA (10).

In the ACOSOG Z1071 trial, overall FNR was 12.6% and this rate varied based on the number of dissected lymph nodes: 31.5% when 1 SLN was dissected, 21% when 2 were dissected, and 9.1% when more than 3 nodes were dissected.

In the SENTINAL trial, FNR was reported as 24.3% for patients with one node resection and 18.5% for those with two resected nodes.

According to both studies, FNR could be less than 10% when more than 3 SLNs were resected (9, 10).

In the patients of this study, the false negative rate of 0% was achieved. The positive pathological and clinical response was higher in the present study comparing others. Previous studies have reported a positive pathological rate around 40% after neoadjuvant therapy of patients with clinically positive nodes (12). One explanation of this difference can be the limited number of cases in the current study.

4.1. Conclusions

Although previous studies have reported that SLNB after neoadjuvant chemotherapy in patients with breast cancer with positive nodes might have a higher rate of false-negative results, the present study showed that it could be feasible and accurate in this subset of patients.

Acknowledgments

Footnotes

Authors' Contribution: None declared.

Conflict of Interests: Authors disclosed no conflict of interest.

Ethical Considerations: This study is approved by ethical committee of Milad Hospital.

Financial Disclosure: None declared.

Funding/Support: This project has been funded by Milad General Hospital.

Patient Consent: In this study, the methods were in accordance with the national ethical standards involving human subjects and later versions of Helsinki Declaration. The current study was approved by Milad Hospital Ethics Committee. We provided a general information as a consent form and agreement for the usage of their data in medical research. This study used the archived material of patients, who were treated in the hospital in previous years.

References

1. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg.* 1994;**220**(3):391–8. discussion 398-401. doi: 10.1097/00000658-199409000-00015. [PubMed: 8092905]. [PubMed Central: PMC1234400].

2. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: Results from the NSABP B-32 randomised phase III trial. *Lancet Oncol.* 2007;**8**(10):881–8. doi: 10.1016/S1470-2045(07)70278-4. [PubMed: 17851130].

3. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol.* 1998;**16**(8):2672–85. doi: 10.1200/JCO.1998.16.8.2672. [PubMed: 9704717].

4. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *Br J Surg.* 2006;**93**(5):539–46. doi: 10.1002/bjs.5209. [PubMed: 16329089].

5. Lee HD, Ahn SG, Lee SA, Lee HM, Jeong J. Prospective evaluation of the feasibility of sentinel lymph node biopsy in breast cancer patients with negative axillary conversion after neoadjuvant chemotherapy. *Cancer Res Treat*. 2015;**47**(1):26–33. doi: 10.4143/crt.2013.208. [PubMed: 25327493]. [PubMed Central: PMC4296849].

6. Fu JF, Chen HL, Yang J, Yi CH, Zheng S. Feasibility and accuracy of sentinel lymph node biopsy in clinically node-positive breast cancer after neoadjuvant chemotherapy: A meta-analysis. *PLoS One*. 2014;**9**(9). e105316. doi: 10.1371/journal.pone.0105316. [PubMed: 25210779]. [PubMed Central: PMC4161347].

7. Lee S, Kim EY, Kang SH, Kim SW, Kim SK, Kang KW, et al. Sentinel node identification rate, but not accuracy, is significantly decreased after pre-operative chemotherapy in axillary node-positive breast cancer patients. *Breast Cancer Res Treat*. 2007;**102**(3):283–8. doi: 10.1007/s10549-006-9330-9. [PubMed: 17063280].

8. Newman EA, Sabel MS, Nees AV, Schott A, Diehl KM, Cimmino VM, et al. Sentinel lymph node biopsy performed after neoadjuvant chemotherapy is accurate in patients with documented node-positive breast cancer at presentation. *Ann Surg Oncol*. 2007;**14**(10):2946–52. doi: 10.1245/s10434-007-9403-y. [PubMed: 17514407].

9. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;**310**(14):1455–61. doi: 10.1001/jama.2013.278932. [PubMed: 24101169]. [PubMed Central: PMC4075763].

10. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): A prospective, multicentre cohort study. *Lancet Oncol*. 2013;**14**(7):609–18. doi: 10.1016/S1470-2045(13)70166-9. [PubMed: 23683750].

11. Caudle AS, Kuerer HM. Targeting and limiting surgery for patients with node-positive breast cancer. *BMC Med*. 2015;**13**:149. doi: 10.1186/s12916-015-0385-5. [PubMed: 26109042]. [PubMed Central: PMC4481081].

12. Lee HK, Yang HK, Kim WH, Lee KU, Choe KJ, Kim JP. Influence of the number of lymph nodes examined on staging of gastric cancer. *Br J Surg*. 2001;**88**(10):1408–12. doi: 10.1046/j.0007-1323.2001.01875.x. [PubMed: 11578301].