Original Article

Diagnostic accuracy of sentinel lymph node biopsy in determining the axillary lymph node metastasis

ABSTRACT

Background: Sentinel lymph node biopsy (SLNB) is accepted as the standard procedure to determine the axillary lymph node metastasis in breast cancer at early stage. However, in many cases with sentinel lymph node positivity, the axilla does not contain any tumor cells. As a result, the accuracy of SLNB to predict axillary lymph node metastasis must be evaluated.

Patients and Methods: Thousand hundred and fourteen women operated for breast cancer were retrospectively examined. Breast cancer patients without axillary metastasis on clinical examination who had undergone SLNB were included in the study. Sentinel lymph node positivity and axillary lymph node positivity were compared.

Results: Among 1114 women operated for breast cancer, 230 were clinically node negative preoperatively and undergone SLNB. Eighty-three (36%) of the patients were SLNB positive and undergone axillary dissection. Forty-three (51.8%) of them had tumor positive axillary lymph nodes and 40 (48.2%) of them had tumor negative axillary lymph nodes.

Interpretation: In 48.2% of the patients, positive sentinel lymph node does not demonstrate a positive axilla. This finding supports sparing axillary dissection in patients with favorable prognostic factors even if the sentinel lymph node is found to be positive.

Conclusion: Axillary lymph node dissection(ALND) may be spared even if there are macrometastatic sentinel lymph nodes in patients with favorable tumor types who will undergo breast-conserving surgery.

KEY WORDS: Axillary lymph node metastasis, early breast cancer, sentinel lymph nodes

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INTRODUCTION

There are two types of lymphatic vessels in the breast: superficial and deep lymphatics. Superficial lymphatics drain to the deep lymphatics and lymph from the deep lymphatics flows toward the internal mammarian and axillary lymph nodes. About 3% of the lymph drain to the internal mammary nodes and the rest (97%) of the lymph drain to the axillary lymph nodes.[1] Lymphatic mapping and sentinel was first reported in 1977 by Cabanas for penile cancer. He studied one hundred cases using lymphangiograms, anatomic dissection, and microscopic evaluation. He demonstrated the existence of specific lymph node center called sentinel lymph node which is the first site of metastasis from penile carcinoma. Lymphatics never drained into the iliac or inguinal and femoral lymph nodes before they had drained into sentinel lymph nodes.[2] Most neoplasms have the ability to metastasize via the lymphatics, and therefore, in oncologic operations, the primary tumor and the draining lymphatics are removed en bloc. This type of surgery is carried out when the lymph nodes draining the primary tumor site are adjacent to tumor bed as colorectal cancers and gastric cancers. For tumors in which regional lymph nodes not immediately adjacent to the tumor (e.g. melanomas and breast cancer), lymph node surgery is performed through a separate incision.[3]

For patients who have early breast cancer and are clinically node negative on physical and radiologic studies, the sentinel lymph node is used to determine the axillary lymph node metastasis.[4]

Axillary lymph node metastasis progresses regularly from the first to the second, then to the

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third lymph node.[5] If the sentinel lymph node is clear of tumor cells, then axillary lymph nodes are accepted as clear. If SLN contains tumor cells, axillary dissection is recommended under certain circumstances discussed below. In our study, we evaluated the value of sentinel lymph node biopsy (SLNB) in determining the positive lymph nodes in the axilla. We know that negative SLNB means negative axilla. We analyzed if positive sentinel nodes can predict positive axillary lymph nodes.

PATIENTS AND METHODS

Patients

The study was approved by the ethics committee. It was a single-center retrospective study. We studied 230 patients with operable breast carcinoma from January 2007 to January 2019. Patients with c T1–T3 and c N0 patients were included in the study. We excluded patients with clinically positive lymph nodes.

The youngest patient was 29 years old and the oldest patient was 84 (mean 54.96 ± 11.88) years old. The tumor size, measured on pathological sectioning, ranged from 0.7 cm to 12.5 cm. Characteristics of 83 patients are summarized in Table 1.

Surgery

Sentinel lymph node dissection is carried out with the aid of blue dye (isosulfan blue or methylene blue). Five milliliter of blue dye is injected in the subareolar plexus. After 5 min of breast massage toward the axilla, a 3–4 cm incision is made in the lower axilla just below the hairline. After dissecting through subcutaneous tissue, the axillary fascia is dissected and blue lymphatic channels are followed. Following these channels leads to sentinel lymph node.[4,6]

The node is sent to the pathology laboratory for frozen section analysis. İf macrometastasis, i.e., ≥2 mm metastasis, is found, then SLNB is followed by axillary dissection. In case of negative SNLB or micrometastasis, axillary lymph node dissection (ALND) is spared.

Table 1: Characteristics of 83 patients

Patient Characteristics	Findings
Age	54.96±11.88
TM size	
<2	26 (31.3)
≥2	57 (68.7)
Hormone receptor	
–	10 (12)
+	73 (88)
Ki 67 index	
<7%	24 (31.6)
≥7%	52 (68.4)
SNLB number	1.90±1.29
Metastatic SLN number	
1	60 (72.3)
2	15 (18.1)
3	6 (7.2)
4	2 (2.4)
ALN metastasis	
–	40 (48.2)
+	43 (51.8)

SLN=Sentinel lymph node, TM=Tumor, SNLB=Sentinel Lymph Node Biopsy, ALN=Axillary Lymph Node

Pathological examination

Sentinel node frozen section examination

The size of the node or nodes was recorded. Each node was thinly sliced along the long axis of the node at 2 mm, and all slices were submitted for frozen section examination. At least one representative hematoxylin-and-eosin (H and E) level was examined.

Permanent examination of negative sentinel node

After the frozen section examination, all slices of the node of nodes were submitted for tissue processing. At least 10 representative H and E levels were examined. Immunohistochemical study (pancytokeratin) was performed to the second and eighth levels. Size of metastases and the presence of extranodal tumor invasion were recorded. Only the largest contiguous focus of tumor in the node evaluation was used for classification.

Statistical analysis

The purpose of our study is to find out the percentage of patients with axillary lymph node metastasis, whose sentinel lymph node is positive. We studied 83 patients having a positive sentinel node. The data were calculated as mean ± standard deviation, numbers, and % frequencies. The relation between axilla(+, -) = axillary lymph node involvement, tumor size, hormone receptor status, cERB2, Ki 67, and SLNB numbers was calculated using Chi-square or Fischer's exact test, and the relation between sentinel lymph node numbers was calculated using Mann–Whitney U-test. The Pearson chi square test results were shown by "%," and Mann–Whitney-U test results are shown by "Min-Max." Statistically, meaningful value is accepted as $P < 0.05$, and the data were calculated using IBM Corp., Released 2013, IBM SPSS for Windows, version 22.0 (Armonk, NY: IBM Corp,USA).

RESULTS

Between January 2007 and January 2019, 1114 patients underwent breast cancer surgery. Two hundred and thirty of them who had clinically negative axilla underwent SLNB. Eighty-three patients were SLNB+ and underwent ALND. The aim of the study was to determine the accuracy of SLNB in predicting the presence of axillary lymph node metastasis. Forty patients (48.2%) had a negative axilla and 43 patients (51.8%) were positive for axillary metastasis. The age of the patients ranged between 29and 84 years (mean: 54.96 ± 11.88). The pathology of breast cancer was invasive ductal carcinoma in 70 patients. Eight patients had lobular carcinoma, four patients had mucinous carcinoma, and one patient had carcinosarcoma. The smallest tumor diameter was 0.7 cm and the largest tumor size was 12.5 cm. Tumor size was <2 cm in 26 (31.3%) patients and ≥2 cm in 57 (68.7%) patients. Ki-67

Table 2: Patient characteristics and axillary lymph node involvement

	ALN metastasis		*P*
	–	+	
TM size			
<2	15 (37.5)	11 (25.6)	0.242[a]
≥2	25 (62.5)	32 (74.4)	
Hormone receptors			
–	4 (10)	6 (14)	0.740[b]
+	36 (90)	37 (86)	
Ki-67 index (%)			
<7	14 (38.9)	10 (25)	0.193[a]
≥7	22 (61.1)	30 (75)	
SNLB numbers			
1	32 (80)	28 (65.1)	0.280[a]
2	5 (12.5)	10 (23.3)	
3	3 (7.5)	3 (7.0)	
4	0 (0.0)	2 (4.7)	
SNLB metastasis	2 (1-7)	1 (1-5)	0.161[c]

[a]Chi-square test, [b]Fisher's exact test, [c]Mann-Whitney U-test. TM=Tumor, SNLB=Sentinel Lymph Node Biopsy, ALN=Axillary Lymph Node

proliferation index was <7% in 24 (31.6%) patients and ≥7 in 52 (68.4%) patients. 10 patients were hormone negative and 73 patients were hormone positive. These findings are summarized in Table 2.

DISCUSSION

Breast cancer prognosis depends on two factors: tumor size and axillary lymph node involvement. These two important factors act as independent but additive parameters. Five-year survival rate varies from 45.5% for tumors >5 cm with positive axilla to 96.3% for tumors <2 cm with negative axilla.[5]

Breast cancer treatment is tending to be less invasive and more targeted. The acceptable surgical margin is "no ink on tumor" for both invasive breast carcinoma and ductal carcinoma *in situ*. Surgery of the axilla is also being questioned. ALND can be omitted in patients with one or two macrometastatic lymph nodes if postoperative radiotherapy is planned.[6]

Axillary lymph node involvement is important in postoperative treatment planning and follow-up. In the past decades, ALND is decreasing progressively. Sentinel lymph node sampling is used instead of ALND in early-stage breast cancer patients without clinical axillary involvement.[7,8]

Buscombe *et al*. explained procedural guidelines to detect sentinel lymph node in breast cancer. Both radiopharmaceuticals and blue dye are used.[9] Although sentinel lymph node is identified using both radioisotope tracer and isosulfan blue, it can be identified using isosulfan blue alone. Brahma studied 96 patients and the identification rate of sentinel lymph node was 91.7%.[10] Özdemir studied 32 patients and the SLN detection rate was 94%.[11] Ang Ch studied 610 patients and the detection rate of SLN was 98%.[12] ALMANAC trial studied 842 patients to detect false-negative rates of sentinel lymph node. Patients with clinically node-negative breast cancer underwent SLNB following the usage of radiopharmaceutical 99m Tc albümin and Patent blue V dye. Sentinel lymph node was identified in 803 (96.1%) of 836 cases. There were 19 false negatives, which resulted in sensitivity of 263/282 (93.3%) and accuracy of 782/803 (97.6%), The SLNs were successfully identified by the blue dye in 698 patients (85.6%), by radioisotope in 698 patients (85.6%), and by the combination of blue dye and radioisotope in 782/815 patients (96.0%). False-negative rate was 10.1% when one SLN was removed and 1.1% when multiple SLNs (≥3) were removed (*P*: 0.01).[13]

Weaver DL studied 3887 patients and in 15.9%, there were occult metastases. Overall survival (*P*: 0.03), disease-free survival (*P*: 0.02), and distant disease-free interval (*P*: 0.04) were significantly different in between two groups, but no statistically significant difference was detected in 5-year survival rates between the two groups; 94.6% in group with occult metastasis and 95.8% in group without metastasis.[14] ALMANAC trial, which is the first large randomized controlled trial that compared SLNB with standard axillary treatment in patients having early breast cancer, studied 829 patients. The trial studied the quality of life over 18 months of postsurgical period. Sentinel group recovered more quickly and had less arm swelling ($P = 0.002$) and less numbness ($P < 0.001$). The findings supported SLNB in early breast cancer.[15] IBCSG trial 23-01, phase 3 randomized controlled trial, studied disease-free survival between patients who underwent SLNB and axillary dissection. The patients in this study had tumors <5 cm and were clinically node negative and had one or more mictometastatic (≤2 mm) SLN. Four hundred and sixty-five patients were randomly assigned to axillary dissection group and 469 patients to nonaxillary dissection group. After the patients followed up of 5 years, they recorded disease-free survival in 69 (87.8%) patients in axillary dissection group and 55 (84.4%) patients in nonaxillary dissection group ($P = 0.16$). The study concluded that axillary dissection could be avoided in patients with limited lymph node involvement.[16]

ALND can be spared in patients who have clear sentinel lymph nodes or limited involvement (i.e., isolated tumor cells or micrometastasis).[7,8] Negative sentinel lymph node reliably demonstrates negative axilla.[4] However, in many cases with macrometastatic (>2 mm) SLNB, the axillary lymph nodes are also negative. We designed this study to evaluate the diagnostic accuracy of sentinel lymph node positivity in determining the axillary lymph node metastasis. We found that among 230 patients who had undergone sentinel lymph node sampling, 83 (36%) was positive which is the similar with 35.5% found in the study of Veronesi *et al*.[17] Of these 83 SLNB-positive patients, 48.2% had tumor negative axilla which is higher than 39.5% found in the study of Veronesi *et al*.[4] According to the ASCO guidelines, patients without SLN metastasis should not receive ALND. Patients with 1 or 2 sentinel lymph node positivity who are going to have breast-conserving surgery with whole-breast radiotherapy should not undergo ALND.[18]

ACOSOG Z0011 trial compared SLNB alone with ALND in women with T1/T2 tumors, <3 positive sentinel lymph nodes who will undergo breast-conserving surgery, and whole-breast radiation. There was no difference in local recurrence, disease-free survival, or overall survival between these two groups.[19]

Although the National Comprehensive Cancer Network (NCCN) guidelines for breast cancer, American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, and American Society of Clinical Oncology (ASCO) guidelines include SLN-positive patients having T1 and T2 breast cancer to avoid ALND, our study included 10 patients with T3 tumor. Three of ten patients had clear axilla and seven of ten patients had metastatic ALN. Despite of this inclusion, we still had 48.2% tumor negative axillary lymph nodes in patients who had macrometastatic SLN.[20,21]

CONCLUSION

ALND may be spared even if there are macrometastatic sentinel lymph nodes in patients with favorable tumor types who will undergo breast-conserving surgery.

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Conflicts of interest
There are no conflicts of interest.

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