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ORIGINAL ARTICLE

Application of sentinel node biopsy in breast cancer patients with clinically negative and positive axilla and role of axillary ultrasound examination to select patients for sentinel node biopsy

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Summary

Purpose: *To evaluate the identification rate and the false-negative (FN) rate of sentinel lymph node biopsy (SLNB) using preoperative axillary ultrasound (AU) in patients with clinically negative and positive axilla and to prove that SLNB could also be performed in clinically axillary positive patients.*

Methods: *Three hundred and fifty seven consecutive T1-2 invasive breast cancer patients with clinically negative or positive axilla were enrolled in our Institution between 2006 and 2011. All patients had preoperative AU, and underwent SLNB followed by breast conserving surgery or mastectomy with level 1, 2 axillary dissection. SLNB was performed using 5 mL of 1% methylene blue. The identification (ID) rate and the FN rate of SLNB were calculated for patients with clinically negative and positive axilla, and for patients with negative AU.*

Results: *Two hundred thirty two patients (65%) were clinically axillary-negative and 125 (35%) were clinically axillary-positive. The ID rates of SLNB were 91 and 89% and the FN rates were 7 and 9%, respectively, in patients with clinically negative and positive axilla. The ID rate of SLNB increased to 94% and the FN rate decreased to 4% after the exclusion of 85 patients (24%) with metastatic lymph nodes on AU.*

Conclusion: *SLNB can be safely applied to T1 tumors regardless of the clinical status of the axilla. Use of AU before SLNB significantly increases the ID rate and decreases the FN rate of SLNB in clinically axillary negative as well as in positive patients.*

Key words: axillary ultrasound, clinically negative axilla, clinically positive axilla, invasive breast cancer, methylene blue, sentinel lymph node biopsy

Introduction

Axillary lymph node dissection (ALND) has traditionally been used to determine the status of axillary lymph nodes that is the most important prognostic factor in breast cancer [1]. However, ALND has a significantly high morbidity, and the majority of patients are node-negative at the time of diagnosis [2]. Therefore, ALND exposes these patients to the complications of this procedure without benefit. SLNB has been reported to accurately predict the status of axillary nodes in patients with clinically negative axilla [3], but randomized trials showed that it has a FN rate of 5-17% compared to axillary dissection [4-7]. American Society of Clinical Oncology (ASCO) [8] and National Comprehensive Cancer Network (NCCN) [9] guidelines and Breast Consensus Conference [10] stated that patients with clinically positive axilla are not candidates for SLNB. Nevertheless, clinical examination of the axilla is notoriously unreliable [11,12] and therefore, the utility of SLNB according to clinical axillary examination is controversial [13,14]. Specht et al. [13] also used SLNB in 106 patients with clinically positive axilla with a 0% FN rate and 100% ID rate; however, only 62 patients underwent ALND in that study. Preoperative fine needle aspiration biopsy or core biopsy of the metastatic axillary nodes on AU was report-

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ed to avoid SLNB in patients with axillary metastasis [15-17]. However, fine needle aspiration biopsy of axillary nodes is an invasive and time-consuming procedure and unpleasant for the patient. AU was also used to decrease the FN rate and to increase the ID rate of SLNB [18]. However, there is no study in the literature that compares the ID and the FN rates of SLNB in patients with clinically negative and positive axilla using preoperative AU.

The purpose of this study was to assess and compare the ID and the FN rate of SLNB both in clinically axillary node negative and as well as positive patients and to see if the use of preoperative AU increases the ID rate and decreases the FN rate.

Methods

The study subjects consisted of 357 consecutive T1-2 invasive breast carcinoma patients who underwent mastectomy or breast conserving surgery between 2006 and 2011 years in Ankara Oncology Education and Research Hospital. Patients with ductal carcinoma *in situ* and with known multicentric/multifocal breast carcinoma, patients who underwent previous axillary surgery or neoadjuvant chemotherapy and patients with fixed and conglomerated axillary lymph nodes were not eligible. Three patients with bilateral breast carcinoma were not included in the study. Clinically axillary positive patients were also eligible as well as those with clinically negative axilla. Diagnosis of breast carcinoma was made by fine-needle aspiration biopsy, tru-cut biopsy, incisional, or excisional biopsy. All patients underwent mastectomy or breast conserving surgery with SLNB biopsy followed by level 1, 2 axillary dissection. Informed consent was obtained from all patients, and the study protocol was approved by the Institutional Board.

An AU at all 3 levels of the axilla was performed by using Hitachi EUB 6500 equipment and 6-13 MHz linear probe in all patients before surgery. Ultrasound findings were classified as negative for disease when no nodes were visible or a lymph node contained echogenic, fat-replaced nodes. Findings were reported as positive for disease when the axilla contained suspicious or frankly metastatic nodes, visualized as ovoid or lobulated, well-demarcated, hypoechoic nodes (>5 mm) [19]. All records were maintained in a prospective database.

Before the study period, all participating surgeons of our team performed at least 30 SLNBs using methylene blue dye for 3 years during the learning curve. Before SLNB incision in the axillary region, 5 mL of 1% methylene blue dye was injected into the subareolar region and into the breast parenchyma around the palpable tumor or excisional biopsy site. After the injection of methylene blue dye, the breast was manually compressed and gently massaged for 5 min. Axilla was exposed through a separate incision approximately 1 cm inferior to the hairline of the axilla [20]. A blue stained node or a blue lymphatic channel that abruptly ended in a palpable node and nodes that were hard and highly suspicious for metastatic tumor without a blue stain were also removed as a sentinel node and sent for frozen section analysis [5]. All lymph nodes were examined by standard hematoxylin-eosin (H&E) staining. For frozen examination SLNs < 5 mm were bisected and stained; those ≥ 5 mm were sectioned at 2 mm slices and single sections were stained with H&E. After frozen section analysis, nodes were embedded in formalin, cut into 4 sections, and stained with H&E. For histopathological examination of non-SLNs removed by axillary dissection, each node was sectioned into 4 slices, stained with H&E, and pathological assessment was performed by two experienced pathologists [21]. AJCC 2002 TNM classification was used for pathological tumor size and nodal status [22].

Information regarding clinical examination of the axilla, age, pathological tumor size and grade, number and histological status of SLNs, the histological status of axillary nodes, types of biopsy, lymphovascular invasion, estrogen (ER) and progesterone receptor (PR) status, and location of tumor in breast were obtained from the medical records of patients.

A positive test was considered as clinically positive axilla, positive findings on AU or a SLN with metastasis on histology. A negative test was considered as clinically negative axilla, negative findings on ultrasound or a SLN with benign histology. True-positive result (TP) was defined as a positive test finding that had a malignant histology, and true-negative result (TN) as a negative test finding that was diagnosed as benign on histology. False-positive result (FP) was defined as a positive test finding that had a benign histology, and FN was a negative test finding that had a malignant histology. FN rate was defined as FN/(FN+TP). Sensitivity was defined as TP results divided by TP plus FN results. Positive predictive value (PPV) was calculated as TP/(TP+FP). Negative predictive value (NPV) as TN/(TN+FN). Accuracy was estimated as (TP+TN)/(TP+FP+TN+FN). ID rate of SLN was defined as the number of patients with identification of at least one SLN divided by the total number of patients. Sensitivity, specificity, FN rate, PPV, NPV and accuracy for SLNB were calculated among patients with a SLN that was successfully identified by methylene blue (Table 1) [23,24].

Statistical analysis

Statistical analysis was performed by Statistical

Table 1. Assessment of true and false negativity, and true and false positivity by comparison of test method with histopathological examination

Test method	*Histopathological examination*	
	Positive	*Negative*
Positive	True positive	False positive
Negative	False negative	True negative

Package for Social Sciences (SPSS) 10.05 for windows. The results were analysed using descriptive statistical methods. Sensitivity, specificity, NPV, PPV, and overall accuracy were calculated by comparing the results of SLNB, AU and clinical axillary examination with the histological findings. The comparisons between proportions were made by chi-square test, and a p-value < 0.05 was considered significant.

Results

The median age of the 357 patients was 49 years (range 26-78). Median tumor size was 2.1 cm (range 0.3-5). Clinical axillary examination showed that 65% of patients were node negative and 35% were node positive. A median of 18 axillary nodes was identified (range 1-43). The median total number of the metastatic axillary nodes was 3 (range 1-28). Axillary dissection revealed that 155 patients (43%) had axillary node metastasis on histology. Clinicopathological characteristics of patients associated with the ID rate and the FN rate of SLNB are shown in Table 2.

Sentinel node identification rate and false-negative rate

SLNs were identified in 322 of 357 patients (SLN ID rate 90.2%). Out of the 322 patients with identified SLNs, positive SLNs were found at definitive histology in 136 patients (42%). There were 11 FN results, and the overall FN rate was 8% (11/136). The median number of SLNs was 2 (range 1-9). Overall accuracy was higher and the FN rate was lower for SLNB compared with clinical axillary examination and AU (Ta-

Table 2. Clinicopathological characteristics of patients associated with the identification rate and the false-negative rate of sentinel node biopsy

Characteristics	*Patient number (%)*	*Identification rate, %*	*p-value*	*False negative rate, %*	*p-value*
Age, years, median					
<40	53 (15)	87	0.57	3	0.09
40-59	213 (59)	90		9.7	
≥60	91 (26)	92		9	
Clinical axillary examination					
Node negative	232 (65)	91	0.58	7	0.76
Node positive	125 (35)	89		9	
Pathologic nodal status					
Node negative	202 (57)	93	0.20	Not	
Node positive	155 (43)	88		applicable	
Pathologic tumor size					
T1	173 (48)	93	0.10	2	0.051
T2	184 (52)	88		12	
Lymphovascular invasion					
Yes	53 (15)	89	0.62	7	
No	304 (85)	90.4		8.4	1.0
Grade					
1	42 (12)	90	0.49	12.5	
2	204 (57)	89		10	0.36
3	111 (31)	93		4	
Estrogen/progesterone receptors status					
Negative	64 (18)	89	0.81	5	
Positive	293 (82)	90.4		8.6	1.0
Tumor location					
Outer quadrant	295 (83)	90	1.0	8.5	1.0
Inner and central quadrants	62 (17)	90		5	
Biopsy type					
FNA or Tru-cut	56 (16)	89	0.80	4	0.68
Excisional/incisional	301 (84)	90		9	

Table 3. Sensitivity, specificity, negative (NPV) and positive predictive value (PPV) and accuracy of clinical axillary examination, axillary ultrasonography and sentinel node biopsy

Method	*Sensitivity %*	*Specificity %*	*NPV %*	*PPV %*	*Accuracy %*	*False negative rate, %*
Clinical examination	50	77	67	62	65	50
Axillary ultrasound	47	94	70	86	74	53
Sentinel node biopsy	92	100	94	100	97	8

ble 3). The ID rate was found to be 93% and the FN rate was 2% for T1 tumors, whereas the ID and the FN rates were 88 and 12%, respectively, for T2 tumors. The FN rate was higher (p=0.051) in T2 tumors compared with T1 tumors (Table 2). SLN ID rate and the FN rate were not significantly different for patients with clinically negative or positive axilla.

Axillary ultrasound findings and SLN identification rate and false-negative rate by ultrasound

AU was negative in 272 (76%) and positive in 85 (24%) patients. Positive and negative AU predicted the presence of metastasis in 73 of 85 (86%) and in 82 of 272 (30%) patients, respectively (p<0.001). Positive AU findings were 17 and 30% in T1, T2 tumors, respectively (p=0.006). AU was positive in 17% of patients with clinically negative axilla and in 37% of those with clinically positive axilla (p<0.001). SLNs were successfully identified in 255 of 272 patients (94%) with negative AU, and in 67 of 85 patients (79%) with positive AU (Table 4). Should the patients with positive AU had been removed from the study or should these patients had undergone ALND without SLNB, the ID rate would increase to 94% for all patients, for clinically node negative and for clinically node positive patients, and the FN rates would decrease to 4% for all patients, to 2.3% for clinically node negative and to 5.4% for clinically node positive patients (Tables 4 and 5).

Table 4. The identification rate and the false-negative rate of SLNB in all patients and in patients with negative axillary ultrasound

	Identification rate, %	*False negative rate, %*
All patients	90.2	8
Patients with negative ultrasound	94	4

SLNB: sentinel lymph node biopsy

Discussion

The findings of our study showed that the ID and FN rates of SLNB were in close range in patients with clinically negative and positive axilla. Although the ID rate was lower (88%) and FN rate was higher (12%) for T2 tumors, our study demonstrated that in patients with T1 tumors, SLNB could be achieved with an ID rate of 93% and a FN rate of 2%, regardless of the clinical axillary status. The findings of the present study also showed that using preoperative axillary AU, the ID rate could be increased, and the FN rate could be decreased to a satisfactory level both in clinically node negative and positive patients.

NCCN [9] and ASCO [8] guidelines have recommended SLNB for breast cancer patients with clinically node negative axilla. However, clinical examination of the axilla has been reported as notoriously unreliable [1,12,25]. Our findings are also consistent with this suggestion, because in our study FN rate, sensitivity and overall accuracy of clinical examination of the axilla were significantly lower compared with SLNB and pathological examination of the axillary nodes. According to ASCO guideline [8] and the Proceedings of the Consensus Conference recommendations [10], patients with clinically positive axilla are not candidates for SLNB due to the likelihood of high FN rate and low ID rate [26]. The findings of the previous two studies [13,24] with clinically positive axilla led to inconsistent results. Specht et al. [13] performed SLNB using a combined blue dye-isotope mapping technique in 106 patients with clinical T1-2 tumors and with clinically positive axilla

Table 5. The identification and the false-negative rates of SLNB by axillary examination in patients with negative axillary ultrasound

Clinical examination	*Identification rate, %*	*p-value*	*False negative rate, %*	*p-value*
Negative axilla	94	1.0	2.3	0.59
Positive axilla	94		5.4	

and reported that the FN was 0% and the ID rate was 100%; however, only 62 patients underwent ALND after SLNB in that study. In another study Bembenek et al. [24] performed SLNB with radiocolloid in 371 patients with clinically negative axilla and in 67 patients with clinically positive axilla. They found that the ID rates were 86 vs. 72%, and the FN rates were 16 vs. 33% for patients with negative and positive axilla, respectively. The results were not significant in multivariate analysis. The metaanalysis by Kim et al. [27] showed that the ID and the FN rates of SLNB were in the range of 41-100% and 0-29%, respectively. The findings of the present study demonstrated that the ID and the FN rates were 90 and 8%, respectively, and were not significantly different for patients with clinically negative or positive axilla.

Our study revealed that T2 tumors were associated with lower ID rate and higher FN rate compared with T1 tumors. The findings of the present study support the study by Bembenek et al. [24] who suggested that SLNB in patients with T2 tumors resulted in a high FN rate compared with tumors ≤ 2 cm (19 vs. 10%). They also found that the ID rates for T1 and T2 tumors were 88 and 82%, respectively. O'Hea et al. [28] reported that the FN rate of SLNB was 18% in T2-3 patients and 2% in T1 tumors. In two studies with tumors >3 cm and in another one with tumors ≥3 cm, SLNB resulted in FN rates of 13, 14 and <5%, respectively [29-31]. In 104 T2-3 tumors (87 T2, and 17 T3) Bedrosian et al. [32] found that the ID rate was 99% and the FN rate 2%. Two large multicentre studies have shown that there is no correlation between tumor size and the FN rates for SLNB [5,33]. However, a Bayesian metaanalysis including 6444 patients with successful SLNBs also found an increased risk for FN results in patients with larger tumors and reported that the chances of missing a positive node for T1a, T1b, T1c, and T2 breast cancers in SLNB were 0.7, 1.5, 3 and 7%, respectively [34], emphasizing thus the findings of the current study. Our study showed that the ID rate was 92% in clinically negative and 95% in clinically axillary positive patients with T1 tumor. The FN rates were 4.5% in the clinically negative and 0% in the clinically positive patients with T1 tumors. So, SLNB could safely be applied in T1 tumors. However, the FN rate in the present study was higher in T2 tumors. The explanation of the association between tumor size and the FN rate is speculative [24]. Large tumor size was known to be associated with increased lymph node metastasis [35]. It is also well known that tumor-replaced lymph nodes may divert the flow of the lymphatic fluid to other uninvolved nodes in the nodal basin, thereby potentially leading to a FN SLNB result [5,36]. Large tumors may derange the concept of the "breast functions as a single unit" by displacing the surrounding lymph channels and generating functionally new lymph channel connections [35].

The findings of the current study demonstrated that the ID rate was 88%, and the FN rate 12% for T2 tumors, respectively. However, among 272 patients with negative AU, the ID rate was 94% and the FN rate 4% for all patients regardless of the clinical examination of the axilla. Moreover, after exclusion of the patients with positive AU, the ID rate increased to 92% and the FN rate decreased to 6.4% in patients with T2 tumors. Use of AU has been shown to increase the ID rate and decrease the FN rate [18]. Our findings support the study of Sato et al. [18] who demonstrated that with preoperative ultrasound evaluation of the axilla, the ID rate increased from 88 to 95% and the FN rate decreased from 8 to 1.7%. They reported that 90% of patients with positive AU had metastatic nodes on histology and among negative AU patients the ID rate was significantly higher and FN rate was significantly lower. However, they did not report the clinical status of the axilla and did not analyse the patients as clinically axillary negative and positive as in the present study.

Limitations

The relatively small size our study and use of methylene blue only, instead of a combination of blue dye and radioisotope for SLNB, are the limitations of our study. Previous studies with methylene blue for SLNB showed a high ID rate over 90% and a low FN rate under 5% in clinically axillary negative patients with T1 [37] or with tumors ≤ 3 cm [37,38]. The review of 69 studies with 8059 patients demonstrated that the proportion of successful mappings was significantly higher and the FN rate was significantly lower in studies in which a radiolabeled colloid was used for mapping [8].

In conclusion, SLNB with methylene blue can be safely applied to T1 tumors both for clinically negative and positive axilla. Use of AU before SLNB significantly increases the ID rate and decreases the FN rate of SLNB regardless of the clinical axillary status. After exclusion of patients with metastatic nodes on AU, SLNB could be performed with an ID rate above 90% and with a FN rate under 10% in clinically axillary negative as well as in positive patients.

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