Original Article

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Biological Subtypes of Breast Cancer and Sentinel Lymph Node Biopsy

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ABSTRACT

Objective: Breast cancer subtypes are used as prognostic and predictive factors considering the genomic profile of the disease. This study is designed to investigate the Sentinel Lymph Node (SLN) detection rate in breast cancer for different biological characteristics.

Material and Methods: Patients on whom we performed the methylene blue method alone were named as Group I, radiocolloid substance method alone as Group II and both methylene blue and radiocolloid method as Group III. The results of biological tumor characteristics and characteristics of the patients on different SLN biopsy techniques were investigated.

Results: The overall SLN detecting success rate was 83.3%. When considered for each group, success rate was 80% for group I, 84.9% for group II and 90.6% for group III. While a success rate of 94.6% was achieved with radiocolloid only in the patients in Luminal A and B subgroup, 90% success rate was achieved in Her2 (+) and triple negative (TN) patients with combined method.

Conclusion: While successful results could be achieved by using radiocolloid substances alone in patients with Luminal A and B subtypes, combined methods should be used in HER2 (+) and TN patients.

Keywords: Breast cancer, methylene blue, radiocolloid, sentinel lymph node biopsy

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Introduction

Axillary lymph node dissection is still part of breast cancer surgery to determine the prognosis and appropriate treatment; however, it is also the most important reason for surgical morbidity. Sentinel lymph node (SLN) concept in practice currently means avoiding axillary node dissection and associated morbidity.

Sentinel lymph node that are negative for tumor cells reflect that the remaining axilla is also tumor-free, there by allowing the surgeon to avoid unnecessary dissection and reduce morbidity. Different techniques are being used to detect axillary SLN's intraoperatively, including vital dyes like isosulfan blue, methylene blue, and patent blue dye, as well as various pharmaceuticals that make lymph nodes visible and easily detectable. Each of these methods have a different success rate for detecting SLN's, and combinations of some methods can increase this rate.

Breast cancer is a heterogeneous disease with distinct clinical and biological features. Subtypes based on the genomic profile of the disease are used as prognostic and predictive factors. The Ki-67 proliferative index and features of the molecular biological subtypes are the most appropriate criteria for the choice of treatment today. Biological differences between tumor groups may affect the technical characteristics related to sentinel lymph node biopsy (SLNB).

The present study was designed to investigate the SLN detection rate in breast cancer based on different biological characteristics of tumors to determine the best SLNB technique for different breast cancer subtypes.

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Materials and Methods

In this prospective study, we evaluated 287 invasive breast cancer patients (250 invasive ductal carcinoma, 21 invasive lobular carcinoma, 9 mucinous carcinoma and 7 invasive tubular carcinoma) between February, 2006 and March, 2010. We performed breast-conserving surgery and SLN dissection to predict axillary involvement. Written consent was obtained from all suitable patients for breast-conserving surgery and SLN dissection.

We classified our patients into subtypes following the Saint Gallen criteria: Luminal A [ER (+) and/or PR (+), HER2- and Ki-67<14], Luminal B [ER (+) and/or PR (+), HER2 (+) and/or Ki-67≥14], Erb-B2 [ER-, PR- and HER2 (+)] and Triple Negative (TN) [ER-, PR- and HER2-] (1).

Table 1. Patient Characteristics in Chi-Square Test According to Biological Subtypes

	Luminal A (100) n (%)	Luminal B (121) n (%)	TN + Her2 (+) (66) n (%)	p
Age				
Age<40	15 (15%)	19 (16%)	14 (21%)	
40≤Age<50	39 (39%)	46 (38%)	24 (36%)	0.08
Age≥50	46 (46%)	56 (46%)	28 (42%)	
Biopsy Method				
Excisional	77 (77%)	83 (69%)	53 (80%)	
Incisional	10 (10%)	18 (15%)	4 (6%)	0.09
Tru-cut and FNA	13 (13%)	20 (16%)	9 (14%)	
Tumor Location				
Upper Outer Quadrant	74 (74%)	87 (72%)	49 (74%)	
Upper Inner Quadrant	12 (12%)	14 (11%)	8 (12%)	0.4
Lower Outer Quadrant	7 (7%)	11 (9%)	5 (7%)	
Lower Inner Quadrant	7 (7%)	9 (8%)	4 (7%)	
Tumor Size				
T1	25 (25%)	31(26%)	17 (26%)	
T2	58 (58%)	69 (57%)	38 (58%)	0.7
T3	17 (17%)	21 (17%)	11 (16%)	
Ki-67				
0-14	21 (21%)	25 (20%)	12 (18%)	
15-30	49 (49%)	50 (41%)	31 (47%)	0.5
>30	24 (24%)	37 (31%)	19 (29%)	
Unknown	6 (6%)	9 (7%)	4 (6%)	
SLNB Technique				
Methylene Blue	64 (64%)	76 (63%)	30 (46%)	
Radiocolloid Substance	17 (17%)	20 (17%)	16 (25%)	0.4
Combined Method	19 (19%)	25 (20%)	20 (29%)	

FNA: fine needle aspiration; SLNB: sentinel lymph node biopsy; TN: Triple negative

We performed three different methods to detect SLN's intraoperatively—methylene blue, radiocolloid substance, and a combined method—and evaluated the success rates of each patient. One of the three SLN detection techniques were applied to the each patient respectively, as methylene blue technique to the first patient, radioisotope colloid to the second patient and combined technique to the third patient, and proceeding to the next patients sequentially.

For the patients whose SLN detection technique would be achieved by methylene blue only or combined technique, 4-6cc of 1% methylene blue solution was applied subdermally to the periareolar and peritumoral region before the surgical procedure started. Following the injection, we waited for 10 minutes and then searched for blue-stained lymph nodes in the axillary region. For the patients whose SLN detection technique would be achieved by radioisotope colloid only or combined technique; 1 mCi Tc-99m nanocolloid was applied peritumorally and/or intradermally 4-12 hours before surgery, and preoperative lymphoscintigraphy was performed on these patients to determine involvement of the lymph nodes.

Lymphnodes detected by gamma detectors or stained blue (either the node itself or the surrounding lymph channels) were considered SLN's. After removal of the SLN, the surgical field was screened again with the gamma detectors and activity less than 10% of the highest (hottest) lymphnode activity was considered back ground activity.

Ethics committee approval was received for this study from the ethics committee of Ankara Oncology Hospital (Decision Date: 12.01.2006, Decision Number: AOH-211/2006).

Statistical calculations were performed using Statistical Packages for the Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Chi-square test is used for comparing patient characteristics (age, menopause status, biopsy and SLNB technique) and tumor characteristics (size, localization, Ki-67 status) with biological tumor subtypes. Logistic regression analysis is used to determine the efficacy of SLNB technique according to biological tumor subtypes and other parameters. The level of significance was set at $p<0.05$.

Results

The study included 287 patients with breast cancer. All the participants were women. The mean patient age was 50.2 years. According to the biological subtypes, 100 patients (35%) were luminal A type, 121 patients (42%) were luminal B type, 43 patients (15%) were TN type, and 23 patients (8%) were Her2 (+) type. Biological subtypes sorted by the patient and tumor characteristics are given in Table 1.

The overall success rate for SLN detection was 83.3% for all patients. We detected at least 1 SLN in 239 of 287 patients and could not find any node in 48 (16.7%) patients. The success rate was 80% for patients whose SLN detection technique was methylene blue only, 84.9% for patients whose SLN detection technique was radioisotope colloid only, and 90.6% for patients whose SLN detection technique was the combined method.

According to patient age, the success rate was 79% (n=34) in patients aged 40 years, 83.4% (n=91) for patients aged 40–50, and 84% (n=114) for patients over the age of 50. The success rate was 84% (n=117) for the premenopausal group and 82.4% (n=122) for the postmenopausal group.

The overall success rate was 83.7% (n=180) for patients who had excisional biopsy primarily, and 78.1%, 83.3%, and 87.5% for incisional, tru-cut, and fine needle aspiration (FNA) biopsies, respectively.

Table 2. Factors Affecting Success Rates in Univariate Analysis

Factor		Success rate (%)	p
Tumor localization	UOQ	84.7	0.09
	UIQ	70.5	
	LOQ	82.6	
	LIQ	90	
Primary biopsy method	Excisional	83.7	0.085
	Incisional	78.1	
	Tru-cut	83.5	
	FNA	87.5	
Patient age	<40	79	0.121
	40-50	83.4	
	>50	84	
Tumor size	T1	80.8	0.41
	T2	86	
	T3	85.7	
Ki-67 proliferative index	0-14	80.3	0.32
	15-30	82.1	
	>30	86.8	
Menopausal status	Premenopausal	84	0.22
	Postmenopausal	82.4	
Biological subtypes	Luminal A-B	86.5	0.02
	TN- Her2(+)	72.8	
SLN detection method	Methylene Blue only	80	0.04
	Radiocolloid only	84.9	
	Combined	90.6	

UOQ: Upper Outer Quadrant; UIQ: Upper Inner Quadrant; LIQ: Lower Inner Quadrant;
LOQ: Lower Outer Quadrant; TN: Triple negative; FNA: Fine Needle Aspiration; SLN: sentinel lymph node

Table 3. Factors Affecting Success Rates in Multivariate Analysis

Factor	p	95% Confidence interval		Odds Ratio
		Lower	Upper	
Biological subtypes	0.014	1.042	5.419	3.57
SLN detection method	0.032	1.351	9.714	2.18

SLN: Sentinel Lymph Node

The overall success rates were 84.7, 70.5, 82.6, and 90% for the upper outer quadrant (UOQ), upper inner quadrant (UIQ), lower outer quadrant (LOQ), and lower inner quadrant (LIQ) tumors, respectively. The overall success rates were 80.8, 86, and 85.7% for T1, T2, and T3 tumors. The Ki-67 proliferative index showed overall success rates of 80.3, 82.1, and 86.8% for tumors with indexes of 0-14, 15-30, and greater than 30, respectively.

Univariate analyses showed that age, menopause status, tumor size, Ki-67 index and tumor localization have no effects on SLNB detection rate. Factors influencing SLNB detection rate is found to be biological tumor subtype and SLN detection method in both univariate and multivariate analysis (Table 2, 3). Because of their biological features and number of patients, luminal A and B tumors and TN and Her2 positive tumors are stratified as two separate groups.

Sentinel Lymph Node could not be detected in 10 of 30 patients (33%) in the Her2 (+) and TN group and could not be detected in 24 of 140 patients (17%) in the Luminal A and B groups when the SLNB was only performed with methylene blue. In patients where the SLNB was performed only with radiocolloid, a SLN could not be detected in 2 of 37 patients in the Luminal A and B groups (5.4%). This rate was 37.5% for patients in the Her2 (+) and TN groups. When the combined method was used, a SLN could not be detected in 9% of the Luminal A and B patients and in 10% of the Her2 (+) and TN groups. When only blue dye or radionuclide was used, SLN detection rate was found to be significantly lower in TN and Her2 (+) groups compared to luminal A and B groups. This difference disappeared when combined methods were used to detect SLN in TN and Her2 (+) patients.

Discussion and Conclusion

Different techniques have emerged to achieve SLN detection. The literature indicates that application of radiocolloid substances and use of gamma probes and lymphoscintigraphy raise the success rates. The present study found a success rate for radiocolloidalone of 84.9% in agreement with the findings of Krag et al. (2) who reported an 82% success rate using a Tc 99m sulfide colloid and a gamma probe in a study of 18 patients. This technique seems easier and less time-consuming than methods using vital dyes. In 1997, Pijpers et al. (3) showed a 97.8% success rate with Tc 99m colloid albumin and concluded that methods with radioactive colloidal substances were better and easier than methods with vital dyes for determining SLN's. In the same year, Veronesi et al. (4) achieved a 98% success rate with radiocolloid alone. Gulec et al. (5) showed a 94%success rate with Tc 99m sulfide colloid alone and concluded that radiocolloid method is less time consuming than vital dye methods. Dunnwald's study with 93 patients reported a rate of 85% (6). The differences in rates between reports are due to the radioactive substance used, its activity, its injection volume, and location of injection.

Pijpers et al. (7) suggested that success rates in malignant melanoma patients could be increased by combining vital dye and radiocolloid methods .Cox et al. (8) confirmed this result for breast cancer in their guideline study, where they found SLN's in 440 of 466 patients (94.4%) with a combined method, and they concluded that a combined method was superior. Liberman et al. (9) suggested that a combined method was superior to the individual methods alone upon achieving a success rate of 91%. Similar to our study findings, in 1999, Hill divided 500 patients into three groups and showed success rates of 80, 85, and 93% for blue dye, isotope, and combined groups, respectively (10).

In our study, we also evaluated the factors that could affect the SLN detection rate, including age, menopausal status, tumor location, size, primary biopsy method, Ki-67 proliferative index, breast cancer subtypes and SLN detection technique. The EORTC 10981-22023 AMAROS study identified 1953 patients who were suitable for SLNB and reported a success rate of 97%. They indicated once again that a combined method was better than the individual methods used alone. They suggested that factors affecting these rates included age, pathologic tumor size, tumor histology, year of the procedure, and preferred method (11). Some reports suggest that SLN detection rates decrease with patient age. McMasters et al. (12) indicated that success rates significantly decreased at ages over 50, while Chakera et al. (13) found similar results at age over 56 and Chagpar et al. (14) reported decreases at age over 60 in a study of 4151 patients. The age-dependent success rates reflect the increase in axillary fat tissue and decrease in of lymphatic flow with age (15), as the increase in fat tissue in lymph nodes with age can decrease the passage of vital dyes or radiocolloid substances (16). Similarly, the AMAROS study reported a decrease in the success rate in patients over age 70, but the highest achieved rates were in patients aged between 50 and 69 years. In our study, the success rate was higher in patients over 50 years old than in younger ones. This difference in age ranges can be attributed to fewer numbers of younger patients in the studies. Koizumi et al. (17) concluded that factors that affect the involvement of radioactive substance in SLN's include the body mass index, age, and menopausal status. In our study, we found no difference among the groups according to menopausal status.

The literature contains some reports suggesting that the primary biopsy method, could affect SLN detection (16). However, Miner et al. (18) found that the primary biopsy method had no effects on SLN, and Marchal et al. (19) came to the same conclusion in 2006. However, patients with a previous excisional biopsy might be expected to show a lower success rate due to disrupted lymphatic flow around the tumoral tissue. Although SLN detection rates were the lowest in patients who underwent incisional biopsy in our study, no significant difference was encountered among different biopsy techniques.

Detection of SLN is relatively more difficult in inner quadrant tumors because of masking of internal mammary nodes by the injection site. The long distance between inner quadrant tumors and axillary lymph nodes also imposes a longer waiting time for the delivery of vital dyes or isotopes to the nodes. Krag et al. (16) showed that the success rates are lower in inner quadrant tumors, independent of the SLN detection technique. Morrow et al. (20) suggested that the highest success rate for SLN's is obtained for upper outer quadrant tumors. In our study group, the best success rate was in the lower inner quadrant, but this could be due to the lower number of patients in that group.

Marchal et al. (19) showed that tumor size has no effects on detection of a SLN. Morrow et al. (20) suggested the same result in their studies. However, all these researchers agreed that the success rates decrease in non-palpable tumors. In our study, the overall success rates did not change according to tumor size.

High tumor grades are correlated with an increase in the number of metastatic nodes. In the presence of metastatic lymph nodes, the lymphatic blockade by tumor cells prevents the flow of dye or radiocolloid. For this reason, the SLN success rate would theoretically be expected to decrease with increases in tumor grade. Hence, Marchal et al. (19) suggested that success rates were lower in patients with lower grade. Currently, the Ki-67 tumor proliferative index is also widely used for tumor grading. In our study, we found no correlation between the success of SLN detection and this parameter.

A number of histological, molecular, and biological characteristics, as well as traditional prognostic factors, are longer decisive in the locoregional treatment of breast cancer (21, 22). We know that TN or Her2 (+) patients carry a higher risk of SLN metastasis than do the patients in the luminal group. This risk can be up to six times greater, especially in TN patients (21). The low SLN detection rates in this group of patients with methylene blue or radiocolloid substances alone could be associated with this high metastasis rate. Lymphatic tumor emboli may be the cause of lymphatic drainage problems. Very successful SLN detection rates were obtained, even with the use of radiocolloid alone, in the Luminal A/B group in the present study.

The effects of breast cancer molecular subtypes on SLN or axillary metastases have been examined in many studies, but their relation to the technical success in SLN detection has not been sufficiently examined. The results of our study with a relatively small number of patients lead us to conclude SLN detection technique and tumor biology as Her2 (+) or TN are significant deterministic factors on SLN detection success rate. More prospective studies with higher numbers of patients are needed in this regard.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Oncology Hospital (AOH-211/2006).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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