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Comparison of the accuracy of isosulfan blue and technetium-99m lymphoscintigraphy to determine axillary lymph node metastasis in breast cancer

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SUMMARY

This study aimed to compare the efficiency of isosulfan blue (ISB) and colloid methods in determining metastatic conditions of axillary lymph node in sentinel lymph node biopsy (SLNB). This prospective study was performed between April 2005 and July 2009 at Gulhane Medical Faculty, Department of General Surgery. A total of 102 female patients diagnosed with breast cancer were enrolled in the clinic of Gulhane School of Medicine. According to the diagnostic protocols of SLN, the patients were divided into three groups as follows: ISB (group I), colloid (group II), and ISB and colloid (group III). SLN was identified in 49 of 52 patients (94.2%) in the ISB group; the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and false negativity (FN) ratio were found to be 90.9%, 75.8%, 96.1%, 55.5%, and 9.1%, respectively. On the contrary, the sentinel lymph node was identified in 38 of 38 (100%) patients in the colloid group; the sensitivity, specificity, PPV, NPV, and FN were found to be 88.2%, 100%, 100%, 91.3%, and 11.8%, respectively. In ISB and colloid groups; SLN was identified in 12 of 12 (100%) patients in the ISB and colloid groups; the sensitivity, specificity, PPV, NPV, and FN were found to be 100%, 100%, 100%, and 0%, respectively. This study showed that the combined methods applied to heterogeneous groups of patients for SLNB in breast cancer cases were minimally invasive and effective and hence could be used for evaluating nodal metastases.

Key words: Isosulfan blue, sentinel node, Tc-99m sulfur colloid

INTRODUCTION

Breast cancer is the most common malignant neoplasm in women, accounting for nearly 31% of all female cancers (1-3). Most patients in developed countries are diagnosed with stages I and II, of which about 65% have no axillary lymph node (ALN) metastasis (4). However, complications such as edema, seroma, injuries of veins and nerves passing through ALN, limitation of arm movements, and pain are noted (5-7). The presence and number of axillary metastatic lymph nodes are the most important prognostic factors in breast cancer (4-7). The results of clinical evaluation of the axillary region are often misleading in approximately one third of patients (7-11). It was determined in 1930 that the lymphatic drainage of the primary tumor was directed to a focal point, from where it spread to other lymph nodes. This first station of lymph node metastasis was called sentinel lymph node (SLN) (12,13). Systematic studies of breast cancer have shown that cancer spreads to one or more SLNs before spreading to other ALNs (14,15). The present study aimed to evaluate axillary sentinal lymph node metastasis for breast cancer diagnosis. The effectiveness of technetium-99 m sulfur colloid, isosulfan blue (ISB), and concomitant use of technetium-99 m sulfur colloid and ISB was compared.

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Figure 1: Peritumoral injection of isosulfan blue.

Figure 2: Isosulfan blue injection: periareolar view.

MATERIALS AND METHODS

This prospective study was performed at Gulhane Medical Faculty, Department of General, Breast, and Endocrine Surgery between April 2005 and July 2009. The ethics committee of Gulhane School of Medicine approved the study on December 2009. Patients were diagnosed with breast cancer, and patients scheduled for surgery were included in the study. The exclusion criteria were as follows: patients aged less than 18 years and patients with distant metastasis; patients with breast skin invasion; and patients with satellite nodules. The history and physical examination was performed for preoperative staging. Also, preoperative ultrasonography was conducted on all patients. All patients aged 40 years and above were evaluated using mammography. The cases considered suitable by the breast–endocrine council were evaluated using MRI. Abdominal ultrasonography and whole-body bone scintigraphy were performed in preoperative assessment on patients diagnosed with breast cancer using physical examination and radiological methods. Distant metastases were evaluated in suspected patients using positron emulsion tomography and abdominal computed tomography. Fine-needle aspiration biopsy (FNAB) or trucut biopsy was performed for preliminary diagnosis of breast cancer. Excisional biopsy was performed for the patients who could not be subjected to trucut biopsy or FNAB. The patients underwent the same operation based on the result of pathological frozen section examination.

Surgical methods

After the preoperative staging, patients with early-stage breast cancer (stage I, IIA, or IIB) underwent lumpectomy, sentinel lymph node biopsy (SLNB), quadrantectomy and mastectomy. The patients whose SLNB revealed metastasis underwent level I–II axillary dissection. Moreover, preoperative information in terms of operative strategy was collected for all patients. SLNB and axillary dissection were used separately for patients who underwent breast-conserving surgery. S-shaped incision and mid-axillary line incision were preferred.

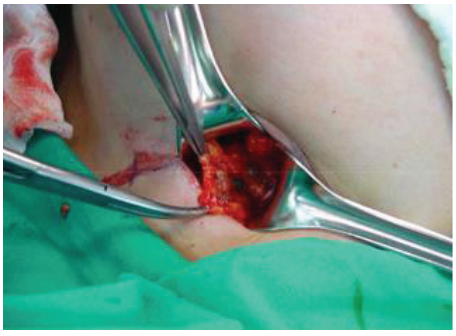

Figure 3: Appearance of dyed sentinel lymph nodes in the axillary region.

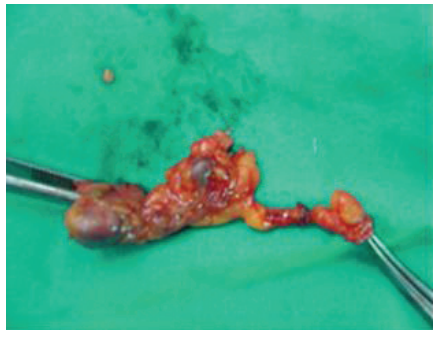

Figure 4: Excision of the lymphatic channels and sentinel lymph nodes.

FIGURE 5: Stewart marked for incision (blue line) and periareolar colloid. Injection sites (red lines).

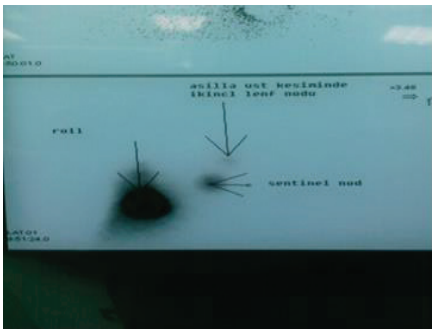

FIGURE 6: Lymphoscintigraphy and SLN localization in Nuclear Medicine.

ISB group

SLN dissection was performed for patients with painted lymphatic ducts in the axillary fatty tissue. Sentinel lymph node metastasis was not detected despite lengthy and detailed dissection in three patients; therefore, these patients were excluded from the study. The excised SLN lymph nodes were sent to the pathology laboratory, for preparing frozen sections. After SLN dissection, breast-conserving surgery or modified radical mastectomy with levels I and II ALN dissection was performed according to surgeon's preference.

Technetium-99m sulfur colloid group

All patients were informed before conducting the operation. They underwent periareolar injection of technetium (Tc)-99m colloid 2 hours before surgery in the Nuclear Medicine Clinic of Gulhane School of Medicine (Figure 5), The injection sites were marked, and breast scintigraphy was performed (Figure 6). Suspicious lymph nodes were identified, and the closest axillary region to the suspicious lymph nodes was marked with a skin marker. The operation was started with an appropriate incision after determining the highest intensity with the gamma probe (the highest 16,000. the lowest 750, and mean 1650 for Tc-99 m sulfur colloid).

Combined method (Tc-99m sulfur colloid and ISB) group

This group received Tc-99 m colloid and ISB injections taking into consideration the application principles.

Statistical analysis

The three methods were compared in terms of sensitivity and specificity. Continuous variables were reported as means and standard deviations. Categorical variables were reported as a proportion or percentage of the total population. Proportions were compared using the Q square or Fisher exact test. Differences between continuous variables were assessed using unpaired t or Mann–Whitney U test. All analyses were performed using SPSS for Windows, version 15 (IBM SPSS). P values <0.05 were considered statistically significant.

RESULTS

A total of 102 female patients diagnosed with breast cancer preoperatively were included in this study. The patients were aged between 30 and 83 years, with a mean age of 52.11 ± 9.57 years.

ISB group

In this group, 39 of 49 patients underwent preoperative mammography. Additionally, breast and axillary ultrasonography was performed on 49 patients. The results of 39 patients who underwent mammography were evaluated using the Breast Imaging Reporting and Data System (BI-RADS). According to the evaluation, BI-RADS 5 was observed in 19 patients, BI-RADS 4 in 18 patients, BI-RADS 3 in 1 patient, and BI-RADS 0 in 1 patient. Based on the pathological diagnosis, FNAB was performed in 32 patients, excisional biopsy in 5 patients, and intraoperative frozen section method in all 49 patients. Isosulfan blue was applied to 52 patients. Further, 49 patients (94.2%) had dyed SLN.

Metastatic SLN was found in 18 of 49 patients (Table 1A and 1B). Further, biopsy revealed 1 SLN in 19 patients, 2 in 17 patients, and 3 in 13 patients, with a total of 92 SLNs and an average of 1.87 SLNs.

Table 1A: In ISB group, distribution chart of cases according to preoperative BIRADS mammography results.

	BI-RADS 5	BI-RADS 4	BI-RADS 3	BI-RADS 0	Total
Preoperative mammography	19	18	1	1	39

Table 1B: In ISB group, distribution chart of cases according to preoperative diagnostic tests.

Axillary node number	Preoperative mammography	ISB performed cases	Dyed sentinel lymph nodes	Cases with metastatic lymph nodes	İİAB	Excisional biopsy	Intraoperative frozen section	Trucut biopsy
49	39	52	49	18	32	5	49	0

One site of SLN metastasis was found in 11 patients. Four patients had 2 sites of SLN metastases, and 3 had 3 sites of SLN, resulting in a total of 28 metastatic SLN. An average of 1.55 metastatic SLN per patient was recorded (Table 2A and 2B). Metastatic SLN lymph nodes were positively detected with axillary dissection without metastasis in one patient. The numbers of metastatic ALN–positive patients was11. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and false negativity (FN) ratio were 90.9%, 75.7%, 96.1%, 55.5%, and 9.1%, respectively (Table 7).

Tc-99m sulfur colloid group

Preoperative mammography, breast ultrasound, and axillary ultrasonography were performed on all 38 patients in this study group. The results of mammography were evaluated using the Breast Imaging Reporting and Data System (BI-RADS). According to the evaluation, 16 patients had BI-RADS 5, 14 had BI-RADS 4, 4 patients had BI-RADS 3, and 4 patients had BI-RADS 0 (Table 3A). For pathological diagnosis, FNAB was used in 22 patients, trucut biopsy in 6 patients, excisional biopsy in 2 patients, and intraoperative frozen section method in 38 patients.

SLN was identified in 38 of 38 patients (100%)in the Tc-99m sulfur colloid group. Metastatic lymph node was found in 15 of 38 patients. Additional axillary metastasis was detected in 15 of 15 patients with metastatic SLN (Table 3B). In two patients, metastatic lymph nodes were detected during axillary dissections without metastases in their SLNB. The sensitivity, specificity, PPV, NPV, and FN were 88.2%, 100%, 100%, 91.3%, and 11.8% (Table 7). Of 38 patients, 1 patient had 8 SLNs, 10 patients had 2, and 27 patients had 3, with a total of 109 SLNs and an average of 2.86 SLNs (Table 4A).

A total of 15 patients had SLN metastasis.; 39 metastatic SLNs were detected. Two of the 15 patients had 1 SLN. Eleven patients had three SLNs. Two patients had two SLNs. Each patient had an average of 2.6 metastatic SLNs (Table 4B).

Table 2A: Number of metastatic and non metastatic total lymph node and distrubition in ISB group.

	One sentinel lymph node	Two sentinel lymph nodes	Threee sentinel lymph nodes	Total sentinel lymph nodes	Mean sentinel lymph nodes
Distribution of cases with sentinel lymph nodes	19	17	13	92	1.87

Table 2B: Number of metastatic sentinel lymph nodes and distrubition in ISB group.

	One sentinel lymph node	Two sentinel lymph nodes	Three sentinel lymph nodes	Number of total cases with metastatic sentinel lymph nodes	Mean sentinel lymph nodes
Number of cases with metastatic sentinel lymph nodes	11	4	3	18	1.55

Table 3A: In Tc 99m sulfur colloid group, distribution chart of cases according to preoperative BIRADS mammography results.

	BI-RADS 5	BI-RADS 4	BI-RADS 3	BI-RADS 0	Total
Preoperative mammography	16	14	4	4	38

Table 3B: In Tc 99m sulfur colloid group, distribution chart of cases according to preoperative diagnostic tests.

Axillary node number	Preoperative mammography	Tc99-m sulfurcolloid performed cases	Tc99-m sulfur colloid–positive lymph nodes	Cases with metastatic sentinel lymph nodes	FNAB	Excisional biopsy	Intraoperative frozen section	Trucut biopsy
38	38	38	38	15	22	2	38	6

ISB and Tc-99m sulfur colloid group

Preoperative mammography, breast ultrasound, and axillary ultrasonography were performed in all 12 patients of this study group. The results of mammography were evaluated using BI-RADS. Two patients had BI-RADS 5, seven patients had BI-RADS 4, one patient had BI-RADS 3, and two patients had BI-RADS 0 (Table 5A). For pathological diagnosis, FNAB was used in 6 patients, trucut biopsy in 1 patient, and intraoperative frozen section method in 12 patients. Further, 2 patients had 4, 4 patients had 3, 4 patients had 2, and 2 patients had 1 SLN, with a total of 30 SLNs and an average of 2.5 SLNs (Table 6A). SLN was identified in 12 of 12 patients in the group (100%). SLN metastasis was detected in 2 of 12 patients. Each patient had an average of one metastatic SLN. At the same time, additional two metastatic lymph nodes were detected in the axillary dissection of these two patients. The number of metastatic additional lymph nodes was two in one patient and one in the second patient. The sensitivity, specificity, PPV, NPV, and FN were 100%, 100%, 100%, 100%, and 0%, respectively, in the colloid and ISB groups (Tables 6B and 7).

DISCUSSION

SLNB has rapidly emerged as a minimally invasive and highly successful method for axillary staging. It has replaced routine ALN dissection as the new standard of care in breast cancer (16). Exact identification of ALNs is required for prognosis and identifying adjuvant treatment modality. Currently, the most reliable method is the removal of all ALNs (complete axillary dissection) and examination of each of them by the pathologist. However, axillary dissection is an invasive procedure with high morbidity. The morbidity rate of SLNB compared with routine axillary dissection is negligible. Moreover, removal and examination of level I and level II lymph nodes yields desired results due to axillary dissection;

Table 4A: Number of metastatic and non metastatic total lymph node and distrubition in Tc 99m sulfur colloid group.

	One sentinel lymph node	Two sentinel lymph nodes	Three sentinel lymph nodes	Eight sentinel lymph nodes	Total sentinel lymph nodes	Mean sentinel lymph nodes
Distribution of cases with sentinel lymph nodes	0	10	27	1	109	2.86

Table 4B: Number of metastatic sentinel lymph nodes and distrubition in Tc 99m sulfur colloid group.

	One metastatic sentinel lymph node	Two metastatic sentinel lymph nodes	Three metastatic sentinel lymph nodes	Number of total cases with metastatic sentinel lymph nodes	Mean sentinel lymph nodes
Number of cases with metastatic sentinel lymph nodes	2	2	11	39	2.6

Table 5A: In ISB and Tc-99m sulfur colloid group, distribution chart of cases according to preoperative BIRADS mammography results.

	BI-RADS 5	BI-RADS 4	BI-RADS 3	BI-RADS 0	Total
Preoperative mammography	2	7	1	2	12

Table 5B: In ISB and Tc-99m sulfur colloid group, distribution chart of cases according to preoperative diagnostic tests.

Axillary node number	Preoperative mammography	Isosulfan blue and Tc-99m sulfur colloid–positive sentinel lymph nodes	Cases with sentinel metastatic lymph nodes	FNAB	Intraoperative frozen section	Trucut biopsy
12	12	12	2	6	12	1

however, the morbidity is close to that of complete axillary dissection when it is performed with radiotherapy (17). The number of lymph nodes removed during axillary dissection depends on a number of factors, most notably the extent of dissection. In the National Surgical Adjuvant Breast and Bowel Project (NSABBP)-B04 study, the average number of lymph nodes removed was between 7 and 30 at different centers. This huge difference between the numbers was based on the surgical technique applied, the experience and tendency of the surgeon, and the ability of the pathologist to evaluate the dissection material (18, 19, 20, 21). In the present study, the number of lymph nodes removed in 44 patients who underwent axillary dissection detected using the ISB method was minimum 7 and maximum 23 (average number 14.2). A total of 247 lymph nodes, including minimum 7 and maximum 21 lymph nodes, were detected from the patients in the colloid group, and a mean of 12.9 lymph nodes was detected per patient. A total of 18 lymph nodes, including minimum 7 and maximum 11, without metastatic and nonmetastatic distinction were detected in 2 patients who underwent axillary dissection in the combined method group; an average of 9 lymph nodes per patient was detected. The number of lymph nodes removed was consistent with the average number quoted in the literature. Complete axillary dissection allows the removal and examination of all lymph nodes. In addition, if axillary metastatic lymph nodes are detected, no additional treatment is required. Some studies advocate that the morbidity rates are comparable to levels I and II dissections, and hence the patients do not receive radiotherapy (22). Completely axillary dissection is the most effective strategy to reduce the risk of recurrence. In the NSABBP-B04 trial, the axillary recurrence risk was inversely proportional to the number of lymph nodes removed and the risk of nodal metastasis increased (20). When levels I and II lymph nodes were excluded, the staging error rate was reported as 2.6%. In a sera of 278 patients who underwent complete axillary dissection, metastases were detected in rotator ganglia and apical

Table 6A: Number of metastatic and non metastatic total lymph node and distrubition in ISB and Tc-99m sulfur colloid group.

	One sentinel lymph node	Two sentinel lymph nodes	Three sentinel lymph nodes	Four sentinel lymph nodes	Total sentinel lymph nodes	Mean sentinel lymph nodes
Distribution of cases with sentinel lymph nodes	2	4	4	2	30	2.5

Table 6B: Number of total cases with metastatic sentinel lymph nodes

	One metastatic sentinel lymph node	Two metastatic sentinel lymph nodes	Three metastatic sentinel lymph nodes	Number of total cases with metastatic sentinel lymph nodes	Mean metastatic sentinel lymph nodes
Number of cases with metastatic sentinel lymph nodes	2	0	0	2	1

Table 7: According to three different methods, distributions of cases diagnosed with SLN and detection of additional axillary involvement.

		Detection of additional axillary involvement			
		ALN positive	ALN negative	Total	P value <0.05
Isosulfan blue	SLN positive	10 (90.9%)	8 (24.2%)	18	0.000
	SLN negative	1 (9.1%)	25 (75.8%)	26	
Tc-99m Sulfur colloid	SLN positive	15 (88.2%)	0 (0%)	15	0.000
	SLN negative	2 (11.8%)	21 (100%)	23	
Combined method	SLN positive	2 (100%)	0 (0%)	12	0.001
	SLN negative	0 (0%)	10 (100%)	0	

lymph nodes in 29 patients (10.4%).(22,23). Considering these residual lymph nodes, it was necessary to apply radiotherapy in cases where levels I and II lymph nodes were removed. This also increased morbidity. Local recurrence was observed in two patients after levels I and II dissections of 259 lymph nodes (24). In the present study, levels I and II dissections were performed in 44 patients following SLNB detected using ISB. Of 17 patients in the colloid group, 2 patients were treated with level I and level II dissections. Dissection of levels I and II lymph nodes in breast cancer was suggested to be curable at the consensus conference of the National Cancer Institute of the United States in 1990 (4). In addition, studies showed that colloid and isosulfan blue methods achieved higher success rates when applied together (25, 26,27).

Although SLNB diagnosis is possible with intratumoral injection, it is not possible in the cases diagnosed using excisional biopsy. The passage of lymphatic circulation is limited in the case of injections into the biopsy cavity (18,28). In the present study, SLN could not be detected in 1 of 12 patients who underwent a preoperative excisional biopsy in the ISB group. Also, SLN could not be detected in one of two patients who underwent a preoperative excisional biopsy in the Tc-99 m colloid group. Wide excisional biopsy showed that the lymphatic channels in the axillary region were destroyed and hence the marker used could not reach this region, especially for tumors located near the region. Tanis and colleagues reported the effectiveness of marker injection using preoperative lymphoscintigraphy before breast cancer surgery as 100%. The effectiveness of lymphoscintigraphy has been shown to be only 32% after performing breast surgery (29). This is one of the reasons for the slightly higher incidence of FN using the colloid method compared with the dye method in the present study. The success rate of SLN detection was lower using the blue dye (74%–87%) than using the radioisotope method (87%–100%), and the success rate (94%–100%) increased when the two techniques were used together (25,26,27). In the present study, SLN were detected in 49 patients in the group treated with ISB (94.23%). SLNs were detected in 38 patients in the colloid group. Further, 12 (100%) SLNs were detected in the third group, in which the 2 methods were applied together. One of the important factors affecting the success rate of the SLNB technique is experience. Certain learning/experience is necessary (30,31) for the team of surgeons, nuclear medical specialists, and cytopathologists to achieve acceptable rates. Negative rates are high in this process (30). The mean number of SLN was 1.87, with minimum 1 and maximum 3 SLNs, in the ISB group. A mean of 2.86 lymph nodes minimum 2 and maximum 8, were detected in the colloid group. In the third group, in which the two techniques were used together, 2.5 SLNs were found on average, with a minimum of at least 1 and a maximum of 4. Cserni found an average of 1.3 SLNs using only vital stains (32). Bass found a mean score of 2.02 in the cohort study of both methods and 1.92 SLNs in Cox regression analysis (33, 34, 35). Although the average number in the present study was higher than the number quoted in the literature, it is believed that the literature figures can be reached with an increase in the number of cases in working groups. The false negative rate was 1 in 26 cases in the group treated with ISB, 2 in 23 cases in the colloid group, and 0% in the combined method group. This ratio was reported

between 0.8% and 11% in various series (32, 33, 35, 36,37,38). It was demonstrated that the false negative rate decreased with the increase in the experience of the surgeon. The average learning curve was 40 (30–45) (39) for 90% success in SLN identification and 5% FN. The mean number of ALNs per patient was found to be 2.81 in patients diagnosed with axillary metastasis. The mean number of axillary metastatic lymph nodes per patient for patients with additional axillary metastases was found to be 2.94 in the colloid group and 1.5 in the combined method group. The average number of metastatic lymph nodes was found to be higher in the colloid group than in the ISB group. This could be explained by unnecessary volumetric removal in SLNB using ISB method. It was believed that the lymph nodes in the region where the radioactivity increased directly could be removed and unnecessary volume excision could be avoided when fixed with the gamma probe. However, the expected time for ISB to spread throughout the lymphatics during the operation varied according to the operator. Nonmetastatic SLNs were also stained in patients who had previously undergone an excisional biopsy in the ISB group. It was concluded that the mean number of metastatic lymph nodes detected using the combined method was lower than the number in the other two groups. This probably depended on the number of patients. No significant relationship has been reported between tumor localization and the success of SLNB (40). However, some studies have shown that the tumors located in the internal quadrant negatively affect the success of SLNB (19). It is possible to detect internal mammary SLN using preoperative lymphoscintigraphy or intraoperative gamma probe. In the present study, 49 vascular lesions were detected in 49 of 52 patients using only vital dye. SLN was detected in 38 (100%) of 38 patients in the colloid group and 12 (100%) in 12 patients in the combined method group. Approximately 30% of SLN-negative patients had a recurrence within 10 years. As mentioned earlier, 9%–30% of metastases detected by re-examining the lymph nodes with serial sections could not be detected in routine pathologic infertility testing (10, 41) This insufficiency could be removed by reducing the cross-sectional area from the lymph node and by cytokeratin immunohistochemical staining (i.e., specific monoclonal antibody) (41, 42). A learning curve (19, 32) was reported in many related studies. An experienced surgeon who applied both methods together had an SLN detection rate of 94%, whereas this rate was 86% for newly recruited surgeons (43). When only vital stains were used, 58.6% of SLN were detected in the first 50 cases; this rate increased to 72.4% in later cases (45). A surgeon could treat 53 cases with 90% success rate (33). Although only vital stains were used in the present study, 94.23% SLN were detected. The axillary region could be easily explored because the surgeons performing the operation had experience with SLNB. the procedure was performed under general anesthesia, and the axillary dissection was also effective. In patients with SLNB, only SLN metastasis was detected in patients with SLNBl metastases in other lymph nodes (non-sentinel) were not detected. In the present study, additional axillary metastases were detected in 10 of 18 SLN-positive patients (PPD, 55%).

Hence, eight patients underwent levels I and II axillary dissections. However, 15 of 15 patients with SLN in the colloid group had additional axillary metastases (PPD, 100%).

Additional axillary metastases were detected in all patients with SLN in the combined method group (PPD, 100%).

CONCLUSION

This study showed that the combined methods applied to heterogeneous groups of patients for SLNB in breast cancer cases were minimally invasive and effective and hence could be used for evaluating nodal metastases.

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