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Original Article

Efficacy and Significance of Sentinel Lymph Node Identification with Technetium-99m–labeled Tin Colloids for Breast Cancer

Kazuhiko Sato*1, Hoshio Hiraide*2, Minoru Uematsu*3, Kuniyoshi Tamaki*1, Hirofumi Ishikawa*1, Tamio Yamasaki*4, Seiichi Tamai*5, Shoichi Kusano*3, and Hidetaka Mochizuki*1

Purpose: The sentinel lymph node (SLN) is thought to reflect the metastatic status of the remaining axillary lymph nodes in patients with breast cancer. We used technetium-99m–labeled tin colloids to identify SLN. The efficacy and significance of SLN identification using this method were investigated in terms of number, size, location, and tumor metastasis. The efficacy of the emulsion charcoal injection method for the intraoperative visible identification of SLN was also evaluated.

Methods: Twenty-five patients with invasive breast cancer were studied. Under ultrasonographic guidance, technetium-99m–labeled tin colloid particles (3 ml) were injected into 3 sites around the tumor within 3 mm of the margin or into the wall of the excisional biopsy cavity 2 hours before surgery. At surgery, just before the incision, an emulsion of charcoal particles (2.5 ml) was injected into 3 sites of the breast parenchyma surrounding the tumor. All patients underwent mastectomy with axillary dissection to the infraclavicular region. The radioactivity of each dissected lymph node was measured. All axillary specimens were processed in individual blocks for permanent section histopathologic evaluation with H & E.

Results: SLN were defined as lymph nodes with 100 000 or more counts per minute (cpm) in radioactivity after injection of labeled tin colloids. In all 25 patients, SLN were identified (mean, 1.9 SLN/patient; range, 1-4). Since the mean uptake in SLN was 383 124 cpm, but only 884 cpm in non-SLN nodes, discrimination between SLN and non-SLN nodes was easy. Clearly visible lymph nodes with charcoal staining accounted for 83.3% of all SLN, although 21.3% of non-SLN also stained. SLN were located only in the axillary region, but there were no other specific features in the location or size of SLN. The SLN were metastatic in 10 of the 25 patients: in 4, the SLN were the only metastatic nodes whereas in the remaining 6 patients, other axillary nodes were also positive. Fifteen patients with no metastasis in SLN had no tumor involvement in any other lymph nodes. There were no skip metastases.

Conclusion: SLN identified with labeled tin colloids have clinical value in predicting the metastatic status of the remaining axillary lymph nodes in breast cancer.

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Key words: Breast cancer, Axillary dissection, Sentinel lymph node

Breast conserving surgery has become standard, replacing mastectomy for early stage breast cancer. Various institutes have established criteria for performing minimally invasive procedures. However, the method of axillary dissection has not changed. Axillary lymph node dissection (ALND) has been routinely performed in all patients with operable breast cancer. There have been many studies about the relationship between tumor size and axillary lymph node involvement[1]. Some clinicians advocate eliminating routine ALND for some patients who are clinically node-negative women with tumors less than 5 mm or clinically node-negative women older than 65 years of age[1-5]. Axillary lymphadenectomy can sometimes induce complications such as lymphedema of the arm[6]. Moreover, ALND, especially for patients with early breast cancer, tends to be regarded as a staging rather than a therapeutic procedure[7]. However, the extent of dissection necessary for accurate staging remains controversial. When compared with total ALND, dissection of level I nodes alone has a staging error rate of

*1 1st Department of Surgery, *2Research Center, *3Department of Radiology, *4 1st Department of Pathology, and *5Department of Clinical Pathology, National Defense Medical College.
Reprint requests to Kazuhiko Sato, 1st Department of Surgery, National Defense Medical College, 3-2 Namiki, Tokorozawa 359-8513, Japan.

Abbreviations:
SLN, Sentinel lymph node(s); ALND, Axillary lymph node dissection; cpm, Counts per minute; H & E, Hematoxylin and eosin staining; n.s., No significance; SLND, Sentinel lymph node dissection

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about 10-12%; dissection of levels I and II, 2-3%; and blind sampling, 14-45%[8].

The sentinel lymph node (SLN) is the first axillary lymph node draining the primary tumor, which is the node most likely to involve cancer cells that have spread to the axilla. The concept of the SLN was presented by Cabanas[9] more than 20 years ago. A technique to identify SLN was first performed by Morton and colleagues[10,11] using blue dye, and later van der Veen and colleagues[12] used lymphoscintigraphy. In the present study, the efficacy and significance of SLN identification with technetium-99m–labeled tin colloids were assessed. The intraoperative utility visible charcoal emulsion injection was also evaluated.

Patients and Methods

Patients

The study was initiated at the National Defense Medical College Hospital in May 1997 and extended through March 1998. Twenty-five patients with T1-2 and N0-1a breast cancer according to the Japanese Breast Cancer Society Guidelines[13], were enrolled. Multifocal and nonpalpable breast cancer cases were excluded. Informed consent was obtained from all patients, who routinely underwent a modified radical mastectomy. ALND was extended to the infraclavicular region in all cases.

Injection of Labeled Colloids

Under ultrasonographic guidance, 3 ml of technetium-99m–labeled tin colloid particles with a size range of approximately 0.4-5 μm (Nihon Mediphysics, Tokyo, Japan) were injected into 3 sites around the tumor within 3 mm of the margin or into the wall of the biopsy cavity, if present 2 hours before surgery. Immediately prior to surgical incision, an emulsion of charcoal particles (2.5 ml) was also injected into 3 sites in the breast parenchyma surrounding the tumor or into the tumor bed in biopsied patients.

Identification of Sentinel Nodes

Just after routine ALND, the lymph nodes were placed in test tubes with 1 ml of normal saline and the radioactivity of each node was counted by an Auto Well Gamma System (Aloka, Tokyo). SLN were defined as lymph nodes with 100 000 or more counts per minute (cpm) in radioactivity.

Classification of Sentinel Nodes

Axillary lymph nodes were classified into 4 groups according to site (upper-lateral, lower-lateral, upper-medial, and lower-medial). Lateral and medial sites were matched to 1a and 1b regions, respectively, according to the Japanese Breast Cancer Society Guidelines[13]. After complete ALND, the size of the lymph nodes was measured and classified into 3 groups according to longest dimension: S, 0.4 cm or less; M, 0.5-0.7 cm; and L, 0.8 cm or more. Lymph node staining with charcoal was classified in all nodes: staining (−), less than half of the lymph node stained with charcoal; (+), half or more of the lymph node was stained with charcoal.

Pathologic Evaluation

All axillary lymph node specimens were processed in individual blocks for permanent-section histopathologic evaluation with hematoxylin and eosin staining (H & E) .

Statistical Analysis

All data were statistically analyzed using the chi-squared test.

Results

General characteristics of the patients enrolled in this study are presented in Table 1. Three were T1N0, 10 were T2N0 and 12 were T2N1a, according to the Japanese Breast Cancer Society Guidelines[13]. Twenty-two had a palpable tumor on physical examination and 3 had undergone excisional biopsy at other hospitals before entry into this study. All patients underwent modified radical mastectomy and no allergic reaction from the injection of technetium-99m–labeled tin colloid particles or the emulsion of charcoal particles was noted.

The tumor characteristics of the 25 patients are also presented in Table 1. There were no special features in the primary tumors.

Sentinel Lymph Node Identification

In all patients, SLN could be identified. Forty-eight SLN (7.8%) were identified among a total of 619 lymph nodes from the 25 patients (mean, 1.9 SLN per patient; range, 1-4). In all cases, the difference in tracer uptake was sufficient to distinguish between SLN (100 000 or more cpm in

Table 1. Characteristics of the 25 Patients in the Current Study.

Sex (Male/Female)	1/24
Age (yr)	
Median	50
Range	34-68
Menopausal status	
Premenopausal	15
Postmenopausal	9
Clinical stages	
T1N0M0	3
T2N0M0	10
T2N1aM0	12
Tumor sites	
Upper-inner quadrant	4
Lower-inner quadrant	2
Upper-outer quadrant	13
Lower-outer quadrant	6
Tumor size (cm)	
Median	3.4
Range	1.5-5.0
Histologic type	
Invasive ductal	15
Invasive lobular	1
Special subtypes	9
Estrogen receptor status	
Positive	16
Negative	9

Table 2. Distribution of SLN and Non-SLN Nodes in the Axilla

	SLN	non-SLN
Upper-lateral	6 (4.3%)	135 (95.7%) †
Lower-lateral	8 (4.7%)	162 (95.3%) †
Upper-medial	14 (7.8%) *	165 (92.2%)
Lower-medial	20 (20.8%) *	76 (79.2%)
Infraclavicular	0 (0%)	33 (100%)

*$p<0.005$; †$p<0.0001$ (chi-square test).

radioactivity) and non-SLN using the Auto Well Gamma System. The mean uptake was 383 124 cpm in SLN and 884 cpm in non-SLN nodes.

Characteristics of Sentinel Nodes

The distribution of SLN and axillary lymph nodes is shown in Table 2. Among all lymph nodes more SLN were detected in the lower-medial site, 20.8%, compared with other axillary sites, namely the upper-lateral, 4.3% ($p<0.001$), the lower-lateral, 4.7% ($p<0.001$) and the upper-medial, 7.8% ($p<0.01$). No SLN were found in the infraclavicular region. There was no relationship between the site of the primary lesion and the location of SLN (n.s.) (Table 3).

Table 3. Distribution of SLN in the Axilla by Site of Primary Lesions

	Site of primary lesions	
	Inner (n=6)	Outer (n=19)
Lateral	4 (28.6%)	8 (23.6%) *
Medial	10 (71.4%)	16 (76.4%) *

*n.s. (chi-square test).

Table 4. Sizes of SLN and Non-SLN Nodes

	SLN	Non-SLN nodes
S (0.4 cm or less)	10 (3.4%) *	297 (96.6%)
M (0.5-0.7 cm)	19 (9.1%) *	189 (90.9%)
L (0.8 cm or more)	19 (18.3%)	85 (81.7%)

*$p<0.05$ (chi-square test).

Table 5. Lymph Node Staining with Charcoal

	SLN	Non-SLN nodes
Staining (+)	40 (83.3%)	122 (21.4%)
Staining (−)	8 (16.7%)	449 (78.6%)

Staining (+), Lymph node with charcoal in half or more of its area; Staining (−), Lymph node with charcoal in less than half of its area.

The size of SLN compared with that of non-SLN nodes is shown in Table 4. Although the proportion of SLN among all lymph nodes was significantly higher in the M (0.5-0.7 cm in diameter) and L groups (0.8 cm or more in diameter) compared with the S (0.4 cm or less in diameter) group, 20.8% of all SLN were found in the S group.

We evaluated ways to identify SLN with labeled colloids and an emulsion of charcoal particles. Clearly visible lymph nodes were defined as lymph nodes with half or more of their area stained by charcoal. Charcoal staining could clearly be seen not only in SLN but also in other lymph nodes. However, 83.3% of all SLN stained with charcoal, allowing macroscopic identification (Table 5).

Predictive Value of Sentinel Nodes for Metastasis

The SLN were metastatic in 10 of the 25 patients with identifiable SLN; the SLN were the

Table 6. Predictive Value of SLN for Metastasis[a]

	SLN metastasis	
	Positive (n=10)	Negative (n=15)
Metastasis in non-SLN nodes	6	0
No metastasis in non-SLN nodes	4	15

[a]Number of patients.

only metastatic nodes in 4 patients, whereas other axillary nodes were also positive in the remaining 6 patients (Table 6). Fifteen patients had negative SLN, without other lymph node involvement. There were no skip metastasis in any case. The SLN could represent the metastatic status of the remaining axillary lymph nodes.

Discussion

The status of the axillary lymph nodes is one of the most important prognostic factors in patients with breast cancer. However, the indications and proper extent of axillary dissection are controversial. It is not clear that complete ALND has a therapeutic benefit for patients with breast cancer. The value of ALND is an increasingly accurate staging procedure, especially in early breast cancer. SLND is a potential alternative to routine ALND, because SLND is likely to have less morbidity than complete ALND and greater staging accuracy than partial ALND.

Many techniques to identify SLN have been reported. Several institutes have used gamma-probe-guided detection with technetium-99m-labeled sulfur colloids[14,15], antimony sulfide[16], and colloidal albumin[17,18]. However, the technique of identifying SLN with tin colloids has not yet been reported. In the present study, tin colloids were shown to be useful in identifying SLN, which could in turn enhance their prognostic utility. SLN were defined as lymph nodes with more than 100 000 cpm in radioactivity. The mean uptake was 383 124 cpm in SLN and 884 cpm in non-SLN nodes. Since the difference in radioactivity between SLN and the other lymph nodes was large, this cut-off value was accepted. The particle size distribution of the colloids is important for identifying SLN, because the ability of the colloids to run through lymphatic tracts and be trapped in SLN similar to breast cancer cells depends on size. The particle size distribution of sulfur colloids ranges from 0.03-10 μm[19]. In the present study, 85% of tin colloid particles ranged from 0.4-5 μm, 5% were smaller than 0.4 μm, and 10% were larger than 10 μm. The tin colloids cost approximately 2500 yen (approximately $19.00) per patient, which is about only 10% of the cost of colloidal albumin. It is difficult to obtain sulfur colloids and antimony sulfide in Japan. Small hand-held probes are commercially available, such as Neoprobe (Neoprobe Corporation, USA), Navigator (United States Surgical Oncology, USA), and C-Track (Care Wise, USA). Since we successfully identified SLN with Neoprobe after injection of technetium-99m labeled tin colloids (data not shown), it appears possible to identify SLN during surgery.

In this study, there was no relationship between the site of SLN and the location of the primary tumor. However, it is not known whether tumors have a specific SLN contingent on their location in the breast. Ultrasonography is a good way to inject colloids just around the tumor.

For dissection of SLN, charcoal dye was available. Fujii *et al*[20] found that injection of an emulsion of carbon particles was useful in the dissection of lymph nodes for breast cancer operations, because of the easy identification of the nodes. Since the emulsion of charcoal particles rapidly travel through the lymphatic system and remain not only in SLN but also in other axillary lymph nodes, 21% of non-SLN nodes stained in this study. However, the mapping method with charcoal dye is thought to be useful to support the identification of SLN with labeled tin colloids, because 83.3% of SLN which can be detected by a small hand-held probe can be visibly and easily identified during operation.

An important point in the present study is the predictive value of SLN for the tumor involvement of non-SLN nodes. Veronesi *et al*[17,21] reported the small percentage (1.3%) of skip metastasis in 1446 patients with breast cancer. We found no skip metastasis in our study, but our sample size was much smaller. Thus, it is unclear whether the absence of skip metastasis in our study is due to the accuracy of the tin colloids technique or to the small number of patients.

We believe that sentinel-node biopsy is an important step forward in the search for more conservative treatments for patients with breast cancer. The routine use of SLND could decrease the long-term morbidity[6] and the cost of managing patients. Some reports have shown several

advantages of SLN biopsy. Giuliano *et al*[16] and Turner *et al*[22] report that sentinel lymphadenectomy with multiple sectioning and cytokeratin immunohistochemical staining of SLN increases the accuracy of axillary staging in breast cancer compared with routine histologic examination after ALND. Veronesi *et al*[16] examined frozen sections of SLN in patients without clinical involvement of the axilla, whose false negative rate was 17% due to micrometastatic foci.

For patients with early breast cancer lumpectomy with sentinel lymphadenectomy can be performed under local anesthesia in an outpatient clinic. Patients with metastatic involvement of SLN can undergo complete ALND under general anesthesia. This strategy can be safe without false negatives, as demonstrated in the present study. Noguchi *et al*[23] proposed the need for a clinical trial to evaluate the efficacy of sentinel lymphadenectomy in Japan, because the biologic behavior of breast cancer might be different in Western and Japanese populations. After such clinical trials, we expect sentinel lymphadenectomy to become the standard procedure for axillary staging in early breast cancer.

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