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Mammary lymphoscintigraphy with various radiopharmaceuticals in breast cancer

Shigeru IMOTO,* Kohji MURAKAMI,** Hiroshi IKEDA,**
Hiroyoshi FUKUKITA*** and Noriyuki MORIYAMA***

*Division of *Breast Surgery and **Radiology, National Cancer Center Hospital East*
****Division of Radiology, National Cancer Center Hospital*

Sentinel node biopsy (SNB) in breast cancer is a promising surgical technique that avoids unnecessary axillary lymph node dissection. To optimize lymphatic mapping with radiopharmaceuticals, mammary lymphoscintigraphy with 30–50 MBq of technetium-99m-diethylenetriamine pentaacetic acid human serum albumin (^{99m}Tc-HSAD), technetium-99m-human serum albumin (^{99m}Tc-HSA), or technetium-99m-tin colloid (^{99m}Tc-TC) were investigated in 69 cases of primary breast cancer. Dynamic early images were obtained during the first 30 or 40 minutes, and static delayed images were obtained 6 hours after tracer injection. Hot spots as sentinel lymph nodes (SLNs) appeared in 51 of 69 cases (74%): in early images in 27 cases and in delayed images in 24 cases. SLNs were visualized more frequently in 23 of the 26 cases (88%) treated with ^{99m}Tc-HSAD and in 21 of the 24 cases (88%) treated with ^{99m}Tc-HSA than in only 7 of the 19 cases (37%) treated with ^{99m}Tc-TC. In 26 of the 51 cases, SLNs were identified as faint spots in delayed images. There was a significant difference in the first appearance of SLNs on the lymphoscintiscan between 43 cases of dense breast parenchyma and 26 cases of fatty breast parenchyma. These results suggest that ^{99m}Tc-HSAD or ^{99m}Tc-HSA is acceptable for lymphatic mapping, but in cases which have faint spots in delayed images or fatty breast parenchyma, gamma probe-guided SNB may result in failure or misleading false-negative SLNs.

Key words: breast cancer, sentinel lymph node, lymphoscintigraphy, breast parenchyma

INTRODUCTION

THE FIRST lymph nodes draining a particular tumor are referred to as the sentinel lymph nodes (SLNs). The histological characteristics of the SLNs are hypothesized to predict the histological findings in the remaining regional lymph nodes. Lymphatic mapping is the first important step in identifying the SLNs, and the SLN sampling technique is called sentinel node biopsy (SNB). Although SLN detection was first described in penile carcinoma in 1977,[1] SNB has been successfully reported in melanoma and breast cancer since the early 1990s.[2,3] A worldwide feasibility study on SNB in breast cancer is currently under way. In our hospital, SNB with the vital blue dye indigocarmine has been performed since January 1998, and proved feasible and successful.[4] We have also been investigating lymphatic mapping and SNB with technetium-99m-labeled agents. In this report, we analyzed mammary lymphoscintigraphy in breast cancer to evaluate the kinetics of different radiopharmaceuticals available in Japan.

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For reprint contact: Shigeru Imoto, M.D., Division of Breast Surgery, National Cancer Center Hospital East (NCCHE), 6–5–1, Kashiwanoha, Kashiwa, Chiba 277–8577, JAPAN.
E-mail: simoto@east.ncc.go.jp

MATERIALS AND METHODS

We used three different technetium-99m-labeled agents: technetium-99m-diethylenetriamine pentaacetic acid human serum albumin (^{99m}Tc-HSAD), technetium-99m-human serum albumin (^{99m}Tc-HSA), and technetium-99m-tin colloid (^{99m}Tc-TC) (Nihon Medi-Physics Co., Tokyo). Sixty-nine female patients with stage 0–IIIB

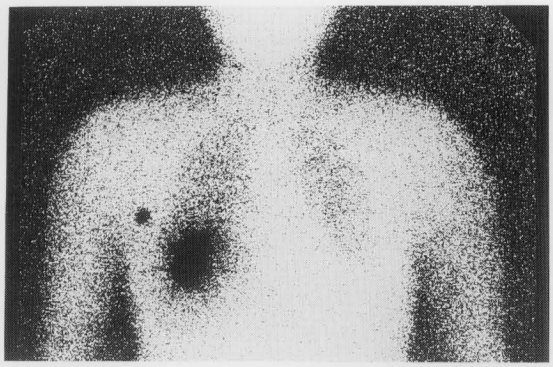

Fig. 1 Visualization of sentinel lymph node (SLN) in early image after ^{99m}Tc-TC injection. The early image in the anterior view clearly demonstrated a hot spot as SLN.

Table 1 Patients characteristics and radiopharmaceuticals

	^{99m}Tc-HSAD	^{99m}Tc-HSA	^{99m}Tc-TC	p value
No. of cases	26	24	19	
Age				
35 or less	2	0	1	0.729
36 to 50	9	10	8	
51 or more	15	14	10	
Histology				
DCIS, LCIS	1	1	0	0.319
IDC, ILC	25	21	19	
Others	0	2	0	
Tumor size (cm)				
2 or less	3	9	3	0.140
2.1 to 5	22	15	16	
5.1 or more	1	0	0	
Clinical stage				
0, I	3	8	2	0.194
IIA, IIB	22	15	17	
IIIA, IIIB	1	1	0	
Nodal metastases				
Negative	15	14	7	0.421
Positive	10	9	12	
Not examined	1	1	0	
Lymphatic invasion				
Ly^-	11	20	11	0.012
Ly^+	15	4	8	

DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma

breast cancer underwent preoperative lymphoscintigraphy with one of the three radiopharmaceuticals between July 1998 and January 1999. Informed consent was obtained before the procedure. The day before surgery, 30–50 MBq (0.8–1.3 mCi) of these agents in 2.5 m*l* of saline was injected subcutaneously at two or three sites around the primary tumor or near the scar after excisional biopsy. Preoperative lymphoscintigraphy of the involved breast and axillary region in the anterior and anterior-oblique

Table 2 Mammary lymphoscintigraphic findings in breast cancer

	^{99m}Tc-HSAD	^{99m}Tc-HSA	^{99m}Tc-TC	p value
No. of cases (%)	26 (100)	24 (100)	19 (100)	
Sentinel lymph nodes				
Visualized	23 (88)	21 (88)	7 (37)	0.009
Not visualized	3 (12)	3 (13)	12 (63)	
Lymphatic channels				
Visualized	12 (46)	13 (54)	3 (16)	0.030
Not visualized	14 (54)	11 (46)	16 (84)	
First appearance of sentinel lymph nodes				
In early image	11 (48)	12 (57)	4 (57)	0.802
In delayed image	12 (52)	9 (43)	3 (43)	
Gamma probe-guided sentinel node biopsy				
Successful	5 (19)	21 (88)	12 (63)	0.001 >
Failed	0 (0)	2 (8)	7 (37)	
Not done	21 (81)	1 (4)	0 (0)	

Table 3 Quality of visualization of sentinel lymph nodes

Change of hot spots from early image to delayed image	^{99m}Tc-HSAD	^{99m}Tc-HSA	^{99m}Tc-TC
[I] faint spots in delayed image			
not visualized→faint spots	6	4	2
faint spots→faint spots	4	4	0
clear spots→faint spots	2	3	0
clear spots→not visualized	0	1	0
Subtotal No. (%)	12 (52)	12 (57)	2 (29)
[II] clear spots in delayed image			
not visualized→clear spots	4	1	1
faint spots→clear spots	1	3	0
clear spots→clear spots	6	5	4
Subtotal No. (%)	11 (48)	9 (43)	5 (71)

projections was performed using a large field scintillation camera (5 minutes-acquisition in a 512 × 512 matrix). Dynamic early images were obtained every five minutes during the first 30 or 40 minutes after tracer injection (Fig. 1), and then static delayed images were obtained 6 hours after tracer injection. The transit time to the first appearance of SLNs and the number of SLNs were recorded. Visualized hot spots were classified as clear or faint spots in early and delayed images.

About 24 hours after tracer injection, total mastectomy or breast-conserving surgery was performed after an SNB. The scintigraphic hot spots *in vivo* were detected with a hand-held gamma-ray detector (Navigator, USSC, USA) or radioactive lymph nodes *ex vivo* were identified with a portable scintillation survey meter. Usually SLNs had 2- to 8-fold radioactivity, compared to non-SLNs as the background, which was counted at around 0.1 μSv/hour by a scintillation survey meter.

Mammography was also performed in all cases at the initial diagnosis of breast cancer. According to modified

Wolfe's classification,[5] mammographic parenchymal patterns were designated by four different classifications: a breast with prominent fat parenchyma as N1, a breast with fat parenchyma and ducts occupying less than 1/4 of the volume as P1, a breast with a prominent ductal pattern occupying 1/4 or more of the volume as P2, and a breast with sheetlike areas of irregularly increased density occupying more than a half of the volume as Dy.

The pathological diagnosis was based on the examination of paraffin-embedded hematoxylin-eosin stained sections of the primary tumor and all axillary lymph nodes.

Statistical significance was determined by means of the chi-square test for differences between the visualization of SLNs and three radiopharmaceuticals, and by means of the paired t-test for the difference of the numbers of SLNs in early and delayed images.

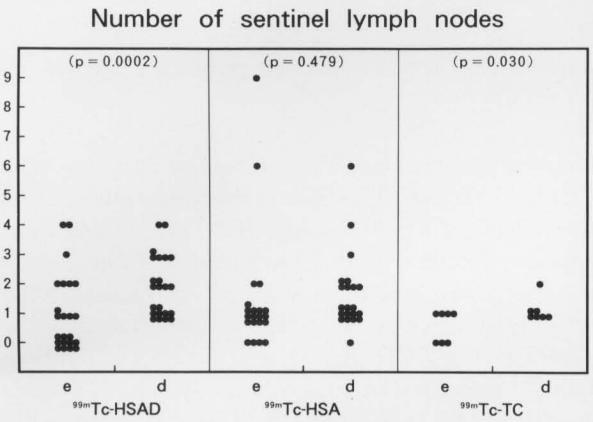

Fig. 2 Comparison of the number of SLNs demonstrated in early (e) and delayed (d) images. The mean number ± standard deviations of SLNs obtained by lymphoscintigrams with ^{99m}Tc-HSAD, ^{99m}Tc-HSA, and ^{99m}Tc-TC were 1.05 ± 1.27 and 1.91 ± 1.0, 1.52 ± 2.11 and 1.71 ± 1.31, and 0.57 ± 0.53 and 1.14 ± 0.38, in early and delayed images, respectively. P value in parenthesis was calculated by the paired t-test between the number of SLNs demonstrated in early and delayed images.

RESULTS

There were no significant differences between the background clinicopathological factors and the use of three radiopharmaceuticals, except for the extensive use of lymphoscintigraphy with ^{99m}Tc-HSA for breast cancer without lymphatic invasion (Table 1). The visualization of SLNs demonstrated with these radiopharmaceuticals is summarized in Table 2. During the early period of this study, a hand-held gamma ray detector was not available in Japan, and gamma probe-guided SNB was not performed in 22 cases. Hot spots appeared in 51 of 69 cases (74%): in early images in 27 cases and in delayed images in 24 cases. SLNs were visualized in 23 of the 26 cases (88%) treated with ^{99m}Tc-HSAD, in 21 of the 24 cases (88%) treated with ^{99m}Tc-HSA, and in only 7 of the 19 cases (37%) treated with ^{99m}Tc-TC. There was no significant difference between the first appearance of SLNs in early and delayed images no matter which of these radiopharmaceuticals was used. ^{99m}Tc-TC visualized significantly fewer SLNs than the other two tracers (p = 0.009). A similar result was seen with the visualization of lymphatic channels (p = 0.030). In 51 of the 69 cases, 49 cases had level I SLNs as hot spots (96%), 5 cases had level II or III SLNs (10%), and the hot spots were

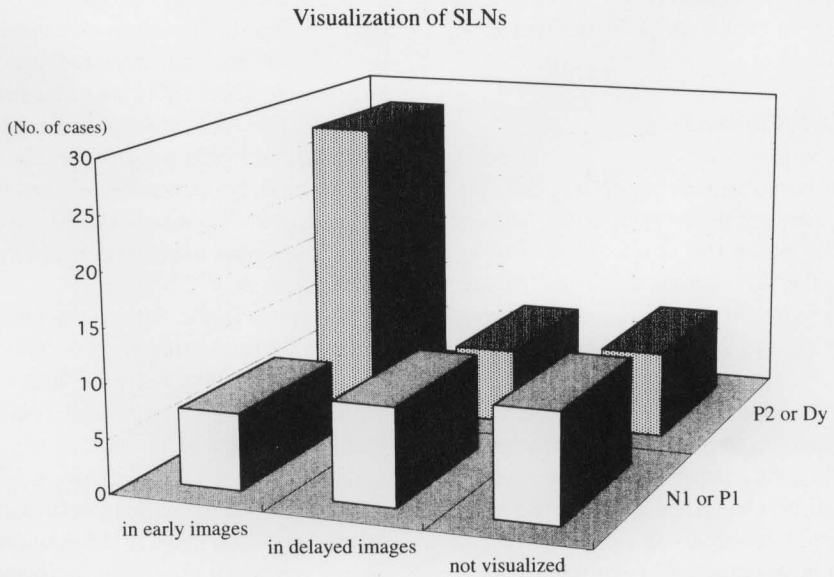

Fig. 3 Visualization of sentinel lymph nodes according to Wolfe's mammographic parenchymal classification. There was a significant difference in the first appearance of SLNs on the lymphoscintiscan between in 43 cases of dense breast parenchyma (P2 or Dy) and 26 cases of fatty breast parenchyma (N1 or P1) (p = 0.009, for the chi-square test).

Table 4 Review of sentinel node biopsy procedures in breast cancer

Author	Isotope	Dose/Saline	Interval to SNB	Injected sites	Probe	Identification rate of SLNs
Krag (3)	S	14.8 MBq/ 0.5 m*l*	1–9 hr	5 sites (peri)	C-Trak	18/22 (82%)
Albertini (6)	S	16 MBq/ ND	2–4 hr	(peri)	Neoprobe	57/62 (92%)
Veronesi (7)	CA	5–10 MBq/ 0.2 m*l*	24 hr	(subderm)	C-Trak	160/163 (98%)
Pijpers (8)	CA	40 MBq/ 4 m*l*	20–24 hr	2–4 sites (peri)	C-Trak	34/37 (92%)
Galimberti (9)	CA	5–10 MBq/ ND	24 hr	ND	ND	238/241 (99%)
O'Hea (10)	S	10 MBq/ 4 m*l*	60 min	4 sites (peri)	C-Trak	52/59 (88%)
Borgstein (11)	CA	40 MBq/ 4 m*l*	21–25 hr	2–4 sites (peri)	C-Trak	122/130 (94%)
Cox (12)	S	17 MBq/ 6 m*l*	1–6 hr	6 sites (peri)	Neoprobe	440/466 (94%)
Barnwell (13)	S	37 MBq/ 4 m*l*	60–90 min	4 sites (peri)	Neoprobe	37/42 (88%)
Krag (14)	S	37 MBq/ 4 m*l*	30 min–8 hr	4 sites (peri)	C-Trak	413/443 (93%)

S, technetium-99m-sulfur colloid; CA, technetium-99m-colloidal albumin; ND, not described; peri, peritumoral injection; subderm, subdermal injection.

parasternal lymph nodes in 6 cases (12%) and extraregional lymph nodes in 3 cases (6%). SLNs were clearly identified in 25 of the 51 cases, whereas 26 of them finally had faint spots in delayed images (Table 3). The mean number ± standard deviations of SLNs identified with ^{99m}Tc-HSAD, ^{99m}Tc-HSA and ^{99m}Tc-TC were 1.05 ± 1.27 and 1.91 ± 1.0, 1.52 ± 2.11 and 1.71 ± 1.31, and 0.57 ± 0.53 and 1.14 ± 0.38, in early and delayed images, respectively (Fig. 2). There was a positive correlation between the number of SLNs in early and delayed images demonstrated with ^{99m}Tc-HSAD and ^{99m}Tc-TC ($p = 0.0002$ and 0.030), but not with ^{99m}Tc-HSA. In 4 cases ^{99m}Tc-HSA hot spots decreased in number in delayed images. According to Wolfe's mammographic parenchymal classification, there was a significant difference in the first appearance of SLNs on the lymphoscintiscan between 43 cases of dense breast parenchyma (P2 or Dy) and 26 cases of fatty breast parenchyma (N1 or P1) ($p = 0.009$) (Fig. 3). In 28 of the 43 cases (65%) of dense breast parenchyma, the SLNs appeared in early images.

DISCUSSION

SNB is performed after lymphatic mapping with vital blue dye, radiopharmaceuticals, or both. The means of identification of SLNs may differ in a number of ways, such as the kind of radiopharmaceutical, the site of tracer injection, the dose of radioactivity used, and the interval between tracer injection and SNB (Table 4).[3,6–14] Many investigators prefer a short interval between tracer injection and SNB, because hot spots are clearly detected with a gamma ray detector. On the other hand, mammary lymphoscintigraphy in breast cancer can help surgeons to know the number of SLNs and an unexpected drainage to Level II, III, or internal mammary chain.[15] Lymphatic mapping and SNB in breast cancer remains standardized. In Western countries, technetium-99m-sulfur colloid and technetium-99m-colloidal albumin are useful for SNB. The sizes of these particles range between 50 and 200 nm, and 3 and 80 nm, respectively.[7,8] Unfortunately, they are not available in Japan. From lymphoscintigrams with ^{99m}Tc-HSAD and ^{99m}Tc-HSA in the present study, SLNs were identified in most cases, but SLNs in half of the cases appeared as faint spots in delayed images at 6 hours after tracer injection. In addition, some hot spots visualized by ^{99m}Tc-HSA injection disappeared in delayed images. The particle size of ^{99m}Tc-HSAD or ^{99m}Tc-HSA is 10 nm or less. ^{99m}Tc-HSA can permeate the lymphatic vessels rapidly, but the radioactivity in SLNs may be gradually reduced in delayed images. Another explanation is that the binding between technetium-99m and HSA in ^{99m}Tc-HSA may dissociate quickly than the binding in ^{99m}Tc-HSAD. It may be difficult to distinguish SLNs from secondary draining lymph nodes (non-SLNs) with gamma probe-guided SNB with ^{99m}Tc-HSA. Lymphoscintigrams with ^{99m}Tc-TC showed clear spots in delayed images, but the rate of identification of SLNs in this series was only 37%, because the median particle (about 500 nm) is too large to migrate through lymphatic vessels easily. Some investigators recommended radiopharmaceuticals with a large particle (200–1000 nm) for mammary lymphoscintigraphy.[16] The ideal radiopharmaceutical for optimized lymphatic mapping needs to be of such a size that it can flow through lymphatic vessels and be retained in SLNs. At present, SNB combined with blue dye (indigocarmine) and a radiopharmaceutical is the best way to identify SLNs in Japan.

Our study is the first to demonstrate a correlation between the transit time to SLNs after tracer injection and breast parenchymal patterns. The numerous lymphatic vessels in dense breast parenchyma allow radiopharmaceuticals to reach SLNs easily.

In conclusion, ^{99m}Tc-HSAD or ^{99m}Tc-HSA is acceptable for lymphatic mapping in breast cancer, but in cases which have faint spots in delayed images or fatty breast parenchyma, gamma probe-guided SNB may result in failure or misleading false-negative SLNs. Although the use of radiopharmaceuticals is limited in Japan, further study is required to determine the standard procedures for mammary lymphoscintigraphy.

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