Tc-99m Diphosphonate as a Potential Radiotracer to Detect Sentinel Lymph Nodes in Patients with Breast Cancer

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Abstract

Purpose To evaluate the potential of Tc-99m diphosphonate as a tracer for sentinel lymph node biopsy in breast cancer.

Methods Lymphoscintigraphs of 35 patients (50.9 ± 10.2 years) with breast cancer were acquired after administering a subareolar intradermal injection of Tc-99m diphosphonate 18 h before surgery. Static images were taken within 15 min (early phase) and 15 h after injection (delayed phase). The lymphoscintigraphic identification rate was defined as the percentage of subjects studied with visible foci at axillae. Sentinel lymph node biopsies were performed using a gamma probe and by blue dye injection. Any node that was radioactive or stained with blue dye was labeled as a sentinel lymph node. Lymph nodes without radioactivity or blue dye staining were defined as non-sentinel lymph nodes. The intraoperative identification rate was defined as the percentage of patients with a radioactive sentinel lymph node. Percentages of lymphoid cells expressing S-100, CD83, and CD1a were compared.

Results The lymphoscintigraphic identification rate was 94.3% (33/35) during the early phase and 96.9% (31/32) during the delayed phase, whereas the intraoperative identification rate was 94.3% (33/35). The mean percentages of lymphoid cells that stained positively for S-100 or CD83 were lower in sentinel lymph nodes than in non-sentinel lymph nodes (1.5% vs. 9.0% for S-100, and 4.5% vs. 9.3% for CD83, respectively, $p=0.0286$). The mean percentages of lymphoid cells in sentinel lymph nodes and non-sentinel lymph nodes expressing CD1a were 3.3% and 7.0%, respectively ($p=ns$).

Conclusions Tc-99m diphosphonate can reliably detect regional lymph nodes in breast cancer.

Keywords Tc-99m diphosphonate · Sentinel node · Breast cancer

Introduction

Axillary lymph node visualization is a common bone scintigraphy finding whenever bone tracer is extravasated in the ipsilateral upper extremity. The frequency of axillary lymph node visualization in routine bone scintigraphy has been reported to be 2% for Tc-99m methylene diphosphonate (MDP). The advantage of Tc-99m MDP in terms of lymph node uptake and bone visualization was first reported by Boxen [1], who suggested the use of Tc-99m diphosphonate for lymphoscintigraphy (Fig. 1 and 2).

Sentinel lymph node biopsy has been widely performed in patients with breast cancer to minimize complications of routine axillary lymph node dissection. Agents used to detect sentinel lymph nodes have included blue dyes or radiopharmaceuticals. The most commonly used radio-

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Fig. 1 Lymphoscintigraphy after a subareolar injection of Tc-99m diphosphonate depicted a focal hot activity (SLN: ⑤) other than the injection site (①) within 15 min of injection in anterior (a) and right lateral views (b). Anatomic information was also provided at 15 h post-injection in anterior (c) and right lateral views (d) due to spontaneous absorption of Tc-99m diphosphonate by bone

pharmaceuticals in Europe and the US are radiolabeled colloids, such as Tc-99m sulfur colloid, Tc-99m antimony trisulfide colloid (ASC), and Tc-99m nanocolloidal albumin [2]. Unfortunately, these radiopharmaceuticals are not always available in Asia. Other proposed radiopharmaceuticals include Tc-99m-labeled dextran, Tc-99m hydroxy ethyl starch, Tc-99m human serum albumin (HSA), Tc-99m stannous phytate, and Tc-99m human polyclonal immunoglobulin G (HIG) [2, 3]. However, commonly available and inexpensive Tc-99m diphosphonate has never been evaluated for sentinel lymph node mapping despite Boxen's suggestion.

Sentinel lymph node biopsy studies have generally been conducted, based on the assumption that lymph nodes

detected by blue dye or radiopharmaceuticals are sentinel [4, 5]. However, recent immunohistochemical studies have stressed several characteristics of sentinel lymph nodes [6]. Sentinel lymph nodes are the first lymph nodes that receive lymph from a primary tumor and thus are most susceptible to metastasis. Furthermore, because lymph nodes closer to a cancer are immunosuppressed by cancer-derived products, this susceptibility is further increased [7]. These immunosuppressed sentinel lymph nodes have reduced paracortical areas and dendritic cell densities [8, 9]. Moreover, mature dendritic cell densities decreased in sentinel lymph nodes, while immature dendritic cell densities increased.

Therefore, the purpose of this study was to evaluate the potential of Tc-99m diphosphonate as a tracer for sentinel

Fig. 2 Immunohistochemical analysis was performed with antibodies to S-100 (**a**, **b**), CD83 (**c**, **d**), and CD1a (**e**, **f**) in sentinel lymph nodes (SLNs) (**a**, **c**, **e**) and non-sentinel lymph nodes (non-SLNs) (**b**, **d**, **f**). Lesser numbers of S-100- and CD83-positive cells were observed in SLNs (**a** and **c**) than in non-SLNs (**b** and **d**)

lymph node mapping in breast cancer by analyzing its identification rate and to confirm these findings by performing immunohistochemical studies.

Materials and Methods

Patients

Thirty-five patients with a clinical diagnosis of T1N0 or T2N0 breast cancer were prospectively enrolled from October 2007 to December 2008. The study was approved by the institutional review board for human research of Kyung Hee University Neo-Medical Center, and informed consent was obtained from all patients. Patients with palpable axillary lymph nodes, regional and/or distant metastasis by radiological studies, such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography with fluorine-18-fluorodeoxyglucose (FDG PET), were excluded, as were patients with a multifocal tumor or medical history of

previous chemotherapy. All of these 35 patients were initially enrolled and underwent early lymphoscintigraphic imaging. However, three patients were not available for delayed lymphoscintigraphic imaging due to overlapping surgical schedules.

Lymphoscintigraphy

In each patient, 111 MBq of Tc-99m diphosphonopropane dicarboxylic acid (DPD) in a volume of 0.4 ml was intradermally injected into the subareolar area of the affected breast 18 h before surgery. Static images were taken in the anterior and lateral positions within 15 min of the injection (early phase) and again 2 h before surgery (delayed phase). Images were acquired with a dual-head gamma camera (Forte, Philips Medical Systems, Milpitas, CA) using a 128 × 128 matrix over 5 min using an all-purpose collimator. Focal areas of increased activity at ipsilateral axillae were marked on the skin with indelible ink.

Lymphoscintigraphic activities were graded visually, as follows: grade 0 was defined as no visible activity; grade 1

as mild activity similar to that of skeletal uptake, and grade 2 as higher activity than that of skeletal uptake.

The lymphoscintigraphic identification rate was defined as the percentage of studied patients (35 for early phase and 32 for delayed phase) with grade 1 or 2.

Intraoperative Sentinel Lymph Node Biopsies

Sentinel lymph node biopsy was performed using a surgical gamma probe (Gamma Finder, World of Medicine, Ludwigstadt, Germany) and intraoperatively by injecting blue dye (Lymphazurin 1%, United States Surgical Corporation, Norwalk, CT). This dye was injected in the subareolar area in the same manner as Tc-99m DPD. All blue-stained nodes were labeled as sentinel lymph nodes (SLNs). Furthermore, all nodes with an *in vivo* radioactive count of ≥ 3 times the axillary background count were also labeled as SLNs. On the other hand, lymph nodes that were not stained or radioactive were labeled non-SLNs. After removing axillary SLNs, operation fields were reevaluated with a gamma probe for residual activity. Non-SLNs were also dissected whenever possible.

Intraoperative identification rate was defined as the percentage of total patients with a radioactive SLN.

Immunohistopathological Analysis

Each lymph node was examined by routine histology with hematoxylin and eosin staining at a minimum of 2-mm intervals. Further immunostaining was performed to confirm that lymph nodes harvested by Tc-99m DPD uptake were sentinel nodes. Paraffin-embedded tissue blocks of lymph nodes from four patients for whom SLNs and non-SLNs were available were evaluated. Immunohistochemical procedures were carried out on 3- μ m tissue sections using the Bond Polymer Intense Detection system (VisionBioSystems, VIC, Australia) according to the manufacturer's instructions with minor modifications. Briefly, 4- μ m sections of formalin-fixed and paraffin-embedded tissues were deparaffinized using Bond Dewax Solution (VisionBioSystems, VIC, Australia), and an antigen retrieval was conducted by treating these with Bond ER Solution (VisionBioSystems) for 30 minutes at 100°C. Endogenous peroxidase activity was quenched by incubating sections in hydrogen peroxide for 5 min. The sections were then incubated for 15 min at ambient temperature with primary polyclonal antibodies for S-100 (1: 80,000, DakoCytomation, Glostrup, Denmark) as a dendritic cell marker, CD 83 (1:100, 1H4b, Novocastra, UK) as a mature dendritic cell marker, and CD1a (1: 1,000, 010, DakoCytomation) as an immature dendritic cell marker using a biotin-free polymeric horseradish peroxidase (HRP)-linker antibody conjugate system in a Bond-max automatic slide stainer

(VisionBioSystems, VIC, Australia). Nuclei were counterstained with hematoxylin. Percentages of immunoreactive cells were assessed for all sections without knowledge of other results. Statistical analysis was performed using the Mann-Whitney U test using MedCalc® 10.1.3.0. Statistical significance was accepted for *p* values <0.05.

Results

The mean patient age was 50.9 ± 10.2 years, and the mean body mass index (BMI) was 23.6 ± 2.8 kg/m². Histological diagnoses of primary tumors were ductal carcinoma *in situ* in 3 patients, microinvasive ductal carcinoma in 1, invasive ductal carcinoma in 25, invasive lobular carcinoma in 2, invasive papillary carcinoma in 1, mucinous carcinoma in 2, and tubular carcinoma in 1 patient. Tumors were located in the upper outer quadrant in 22 patients, in the upper inner quadrant in 7, in the lower outer quadrant in 4, in the lower inner quadrant in 1, and in the retroareolar area in 1 patient. The characteristics of the study subjects are summarized in Table 1.

Lymphoscintigraphic Results after Intradermal Injection of Tc-99m Diphosphonate

The lymphoscintigraphic identification rate was 94.3% (33/35) during the early phase and 96.9% (31/32) during the delayed phase. Grade 0, 1, and 2 percentages during the early phase were 5.7% (2/35), 14.3% (5/35), and 80.0% (28/35), respectively; during the delayed phase, these were 3.1% (1/32), 9.3% (3/32), and 87.5% (28/32), respectively. Individual lymphoscintigraphic grades are presented in Table 1. It should be noted that four patients were upgraded during the delayed phase. Furthermore, one of the four patients benefited from delayed phase imaging due to an upgrade from grade 0 to grade 1.

Results of Intraoperative Sentinel Lymph Node Biopsies

Intraoperative sentinel lymph node detection with the gamma probe and blue dye failed in two patients. Thus, the intraoperative identification rate was 94.3% (33/35). Furthermore, one of these two patients was assessed as grade 0 in lymphoscintigraphy during the early and delayed phases. The other one was assessed as grade 0 in lymphoscintigraphy during the early phase and grade 1 during the delayed phase.

Results of Immunohistopathological Analysis

As routine axillary dissection has been replaced by sentinel lymph node biopsy in our institution, not all the axillary lymph nodes were harvested in our study. There were only

Table 1 Visual lymphoscintigraphy grades and intraoperative sentinel lymph node biopsy results

Patient	Age (years)	BMI ^a (kg/m ²)	Tumor location ^b	Tumor pathology	Lymphoscintigraphic grade		Intraoperative sentinel lymph node biopsy
					Early phase	Delayed phase	
1	44	17.8	UOQ	Tubular carcinoma	2	Not done	Successful
2	35	20.2	LOQ	Mucinous carcinoma	1	1	Successful
3	63	25.9	UIQ	Invasive ductal carcinoma	2	2	Failed
4	43	22.5	UOQ	Invasive ductal carcinoma	0	0	Failed
5	64	23.6	UOQ	Invasive ductal carcinoma	0	1	Successful
6	64	20.8	UOQ	Invasive ductal carcinoma	2	2	Successful
7	44	23.8	UOQ	Invasive ductal carcinoma	1	1	Successful
8	60	26.0	LOQ	Invasive ductal carcinoma	2	2	Successful
9	46	23.1	UOQ	Invasive ductal carcinoma	2	2	Successful
10	43	20.1	UIQ	Ductal carcinoma in situ	2	2	Successful
11	57	20.1	UOQ	Invasive ductal carcinoma	2	2	Successful
12	47	19.8	UOQ	Invasive ductal carcinoma	2	2	Successful
13	41	24.9	UOQ	Invasive ductal carcinoma	2	2	Successful
14	56	29.5	UOQ	Invasive ductal carcinoma	2	2	Successful
15	51	23.3	UOQ	Invasive ductal carcinoma	2	2	Successful
16	53	19.0	UIQ	Invasive ductal carcinoma	2	2	Successful
17	44	24.0	UOQ	Ductal carcinoma in situ	2	2	Successful
18	64	24.4	UOQ	Invasive ductal carcinoma	2	2	Successful
19	44	23.1	UIQ	Invasive ductal carcinoma	2	2	Successful
20	47	23.7	UOQ	Invasive ductal carcinoma	2	Not done	Successful
21	42	29.4	UOQ	Invasive ductal carcinoma	2	2	Successful
22	36	22.9	LIQ	Invasive ductal carcinoma	2	2	Successful
23	53	24.5	UOQ	Invasive papillary carcinoma	2	2	Successful
24	79	25.0	UIQ	Invasive ductal carcinoma	2	2	Successful
25	66	23.2	UOQ	Mucinous carcinoma	2	2	Successful
26	49	21.9	UOQ	Invasive ductal carcinoma	2	2	Successful
27	67	26.8	UOQ	Invasive ductal carcinoma	1	2	Successful
28	44	25.1	LOQ	Invasive lobular carcinoma	1	2	Successful
29	44	22.6	UIQ	Invasive ductal carcinoma	2	2	Successful
30	61	26.2	UOQ	Invasive ductal carcinoma	1	2	Fail
31	50	24.2	UOQ	Microinvasive ductal carcinoma	2	2	Successful
32	44	24.9	UIQ	Invasive lobular carcinoma	2	2	Successful
33	48	26.5	retroareolar	Ductal carcinoma in situ	2	2	Successful
34	39	19.0	UOQ	Invasive ductal carcinoma	2	2	Successful
35	51	27.2	UOQ	Invasive ductal carcinoma	2	Not done	Successful

^a BMI: Body mass index^b UOQ, upper outer quadrant; UIQ, upper inner quadrant; LOQ, lower outer quadrant; LIQ, lower inner quadrant

two patients with metastatic sentinel lymph nodes in our study, and the axillary lymph nodes of these two patients were free from metastatic cells. The false-negative rate was thus in 0% (0/2) in this study.

Percentages of stained cells among lymphoid cells in SLNs and non-SLNs are given in Table 2. The mean percentage staining for S-100 and CD83 was lower in SLNs than in non-SLNs (1.5% vs. 9.0% for S-100 and 4.5% vs. 9.3% for CD83, $p=0.0286$). The mean percentage staining for CD1a

in SLNs and non-SLNs was 3.3% and 7.0%, respectively ($p\geq 0.05$).

Discussion

This study is the first to develop a new sentinel node tracing method based on the old concept that Tc-99m diphosphonate can be taken up by lymph nodes. The

Table 2 Percentages of positive S-100, CD83, and CD1a cells in sentinel lymph nodes and non-sentinel lymph nodes

Patient no.	S-100 ^a		CD83 ^b		CD1a ^c	
	SLN ^d	Non-SLN	SLN	Non-SLN	SLN	Non-SLN
12	3%	15%	7%	12%	5%	2%
15	1%	3%	5%	10%	5%	4%
16	1%	13%	4%	7%	3%	2%
18	1%	5%	2%	8%	0%	20%

^a $p=0.0286$ ^b $p=0.0286$ ^c $p=0.8887$ ^d SLN, sentinel lymph node

identification rate of sentinel lymph nodes by Tc-99m diphosphonate was high enough for clinical use, that is, 96.9% for lymphoscintigraphy and 94.3% for intraoperative gamma probe. Furthermore, immunological studies revealed that nodes harvested after the subareolar injection of Tc-99m diphosphonate were immunologically immature, which suggests that they are sentinel. Because Tc-99m diphosphonate is the most popular radiotracer in nuclear medicine, its potential in detecting sentinel lymph nodes will be practically helpful in the substitution of other radiotracers such as Tc-99m colloids.

The lymphoscintigraphic identification rate of sentinel lymph nodes by Tc-99m diphosphonate (96.9%) was found to be comparable to those by Tc-99m stannous phytate (97%), Tc-99m-labeled dextran (98%), Tc-99m ASC (94–97%), and Tc-99m HIG (94.1%) [5, 11–13]. Furthermore, Tc-99m diphosphonate may also be comparable to Tc-99m tin colloid (89.4%), Tc-99m sulfur colloid (92%), and Tc-99m colloidal albumin (92%) in efficacy [5, 14, 15].

The intraoperative identification rate of Tc-99m diphosphonate (94.3%) was also comparable to those of Tc-99m stannous phytate (95.6–100%), Tc-99m ASC (99.0%), Tc-99m HIG (100%), Tc-99m-HSA (89.5–94.7%), and Tc-99m tin colloid (87.1–96.7%) [5, 13, 16, 17].

Accordingly, our findings indicate that Tc-99m diphosphonate is an excellent alternative for conventional radiocolloids or Tc-99m stannous phytate and Tc-99m HIG. Besides, Tc-99m diphosphonate is readily available at a low cost. Additionally, its use during lymphoscintigraphy offers advantages, such as shorter image acquisition times, because supplementary image acquisition with a flood source is not needed and because it provides more precise anatomic information than the conventional flood source.

The uptake mechanism underlying lymph node detection during bone scanning was initially believed to be a result of colloid formation at the site of extravasation [18]. However, there is no evidence to support the notion that Tc-99m

diphosphonate is colloidal [19]. Subsequently, it was suggested that Tc-99m diphosphonate uptake might be due to a large interstitial injection [19]. Soluble macromolecules, such as Tc-99m HIG have also been used to visualize the lymphatic system [13]. However, its uptake mechanism has not been evaluated.

Tc-99m diphosphonate is a soluble molecule with a comparatively low molecular weight (176 for MDP and 288 for DPD). Thus, the uptake mechanism of Tc-99m diphosphonate may be similar to that of methylene blue dye, which has a molecular weight of 320.

In this study, the identification rate of Tc-99m DPD within 15 min of intradermal injection was comparable to that of blue dye; further, its detection rate was found to be higher at 15 h post-injection [94.3% (33/35) at 15 min to 96.9% (31/32) at 15 h] [20–22]. Interestingly, one patient had an undetectable lymph node at 15 min that was visualized at 15 h, and in three other cases, the lymph node uptake was more clearly visualized after 15 h. These results suggest that the flow of Tc-99m DPD within the lymphatic system is high enough for sentinel lymph node biopsy purposes. Furthermore, the residence time of Tc-99m DPD was greater than that of blue dye, which rapidly exited the lymph nodes [6].

During the immunohistochemical analysis, we sought to confirm that the nodes harvested under Tc-99m diphosphonate guidance were sentinel. This confirmation differentiates this study from previous similar studies whose objective was to determine metastatic lymph nodes [4, 23]. We focused on the maturity of lymph nodes instead of metastatic cell involvement, because we thought that the most important requirement of a sentinel lymph node biopsy is that it should detect sentinel lymph nodes. This is clinically relevant because, for example, the absence of metastatic cells in a lymph node is clinically valuable only if the node were truly sentinel.

Immunohistochemical staining was only performed in four patients with available SLN and non-SLN tissue samples. Staining revealed that there were fewer S-100 positive cells in SLN than in non-SLN tissues, which suggests a reduced dendritic cell density in SLNs [6]. This was further supported by our immunohistochemical findings for CD 83, as fewer CD 83-positive lymphoid cells were observed in SLNs, which is consistent with the results of Huang et al. [10]. This result shows that SLNs contain fewer mature dendritic cells than do non-SLNs. However, we only found a marginal increase in the numbers of immature dendritic cells that express CD1a in SLNs. Furthermore, in one case a SLN showed reduced CD1a expression (patient no. 18). We attribute this unexpected phenomenon to an early disease stage in our patients, which suggests that fewer cytokines are released by tumor tissues during this stage. This topic warrants further study.

This was limited by the small number of tissue samples available, which prevented our reaching statistically meaningful conclusions based on our immunohistochemistry results. This limited sample availability was due to an ethical problem associated with unnecessary dissection; in some cases, it was not possible to harvest lymph nodes selectively.

In conclusion, Tc-99m diphosphonate, the current radiopharmaceutical of choice for bone scanning, was found to allow the reliable detection of regional lymph nodes in breast cancer patients and the identification of sentinel lymph nodes.

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