Reproducibility of Lymphoscintigraphy for Lymphatic Mapping in Cutaneous Melanoma

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One of the indications for lymphoscintigraphy in patients with melanoma is to determine the lymphatic drainage pattern and position of the first draining lymph node—the sentinel node. Metastasis in the sentinel node indicates the need for therapeutic lymph node dissection. The purpose of the present study was to examine the reproducibility of lymphoscintigraphy in assessing the location and number of sentinel nodes. **Methods:** Twenty-five patients with clinically localized melanoma were investigated. The same investigator performed two scintigraphic studies with a 2–4-wk interval in each patient, in an identical manner. A 60-MBq dose of ^{99m}Tc-nanocolloid was injected intradermally at the primary tumor site. The lymph flow was studied dynamically, complemented by lateral/oblique views. The images were evaluated by a panel of three observers. **Results:** The sentinel node was visualized within 20 min in all patients. A difference in number of sentinel nodes depicted on the first and second study was noted in three patients (12%). The melanoma was situated on the head (two patients) and arm (one patient) in these patients. Otherwise, the images were identical for number and location of nodes. **Conclusions:** Reproducibility of lymphoscintigraphy with ^{99m}Tc-nanocolloid was high in this study. However, some sentinel nodes may be missed in lymphoscintigraphy for melanoma.

Key Words: lymphoscintigraphy; melanoma; sentinel node

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The majority (90%) of patients with a melanoma of the skin present with a clinically localized lesion without evidence of metastases in the regional lymph nodes or at distant sites (*1*). However, approximately 20% of these patients do have clinically undetectable micrometastases in the lymph nodes (*2,3*). With these metastases present, the 5-yr survival rate is approximately 50% (*2,4–6*), which decreases to 30% once the affected nodes become palpable (*2,4,5,7*).

The value of elective lymph node dissection remains debatable (*8*). The results of (disputed) prospective and retrospective studies are conflicting (*9–14*). The results of two recently closed prospective studies on the subject are eagerly awaited.

Another approach to the management of regional lymph nodes was developed by Morton et al. (*15*). They hypothesized that early metastasis of melanoma would most likely be situated in the first draining lymph node—the sentinel node. Assuming that lymphogenic metastases often precede hematogenic metastases (*16–18*), and that dissemination in the regional lymph node basin is a sequential process, the presence of metastases in the sentinel node would indicate the need for a regional lymph node dissection. Data supporting this hypothesis have recently been reported by others (*19*).

Meticulously performed lymphoscintigraphy is crucial for reliable sentinel node biopsy. This technique of lymphatic mapping indicates the draining regional lymph node basins, the number of sentinel nodes and their exact location. Although sensitivity and interobserver variability of lymphoscintigraphy are reported to be favorable (*20*), various other aspects also determine the accuracy of an imaging technique. The purpose of the present study was to examine the reproducibility of lymphoscintigraphy in assessing the location and number of sentinel nodes.

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MATERIALS AND METHODS

Patients

From September 1994 to March 1995, lymphoscintigraphy was performed in 25 patients (9 men, 16 women; mean age 46 yr, range 21–69 yr) who were scheduled for lymphatic mapping and sentinel node biopsy for melanoma. Patients were entered according to the criteria described in Table 1. The primary lesion was situated on the lower extremity in 10 patients, on the trunk in 8, on the arm in 4 and on the head in 3. The mean Breslow thickness of the melanomas was 2.5 mm (range 1.1 to 6.5). Ulceration was present in four melanomas.

In no patient was the primary lesion still present at the time of scintigraphy. In 21 patients a diagnostic excision with a small margin (2–5 mm) had been performed. The remaining four patients had undergone therapeutic excision with a margin of 1–1.5 cm. None had received a split skin graft.

Informed consent was obtained from all patients, and the study protocol was approved by the Ethical Committee of The Netherlands Cancer Institute.

Imaging

Technetium-99m-nanocolloid (Solco Nuclear, Birsfelden, Switzerland) with a particle size less than 80 nm was used in a dose of 60 MBq and an average volume of 0.25 ml. Distribution of particle sizes was similar in the different batches. An intradermal route of administration was used with the patient under the gamma camera. In 21 patients the tracer was divided into four portions and administered on each side of the biopsy wound at a distance of 5 mm from its center. In the remaining four patients with smaller wounds, the tracer was divided over only two symmetrical sites. Images were produced using a dual-head gamma camera with a medium-energy, general-purpose collimator. Injection of the ^{99m}Tc-nanocolloid and the following lymphoscintigraphic studies were performed by the same investigator (BAEK) at all examinations.

Immediately after injection, dynamic acquisition at one frame per minute in a 128 × 128 × 16 matrix was started for a period of 20 min to study lymphatic flow. Acquisition was continued for another 20 min when it was uncertain whether the accumulation of radioactivity represented a lymph node or segment of a lymphatic duct. Subsequently, anterior and lateral static views with an acquisition time of 300 sec in a 256 × 256 × 16 matrix were obtained using a ^{57}Co flood source (calibration 11–92: 384 MBq) with a photonenergy peak of 122 keV, as in combined transmis-

TABLE 1
Criteria for Lymphatic Mapping and Sentinel Node Biopsy

Histologically proven primary melanoma
Melanoma preferably excised with a small (2 mm) margin
Excision <3 mo previously
Breslow thickness ≥1 mm
No skin graft
No pregnancy

sion–emission imaging, to facilitate orientation (*21*). The location of the sentinel nodes was marked on the skin with a dye. At 2 hr after injection, a total-body image was made with a camera running speed of 6 cm/min. Oblique views were obtained if there was a possibility that the nodes could be obscured by radiation from the injection site.

Two to four weeks later, on the day before operation, the previous procedure was repeated in an identical manner by the same investigator.

Data Interpretation

The images were evaluated by a panel of three investigators (B.A.E.K., R.A.V.O., O.E.N.) for similarity of the following parameters: lymphatic flow pattern, draining lymph node basin and location and number of sentinel nodes.

Designation of the lymph nodes was done on the basis of dynamic imaging. The lymph node in direct lymphatic connection with the injection site was labeled the *sentinel node. Second-echelon nodes* receive drainage from a sentinel node. These were often visualized on the images but were not evaluated in the present study.

RESULTS

In 22 (88%) of the 25 patients, the first series of lymphoscintigrams was identical to the second series. In three patients differences were observed between both sets of images (Table 2). The sentinel nodes were visualized within 20 min after administration in all studies.

In 21 patients, drainage to a single regional basin was observed. One patient harbored sentinel nodes in three and another patient in four different basins. In two other patients, drainage was found from the primary tumor site to sentinel nodes outside the known lymph node basins: half-way down the thigh in one patient and over the scapula in the other. The repeat images showed drainage to the same regional basins in all patients.

A difference in the number of visualized sentinel nodes, however, was observed in three patients. These three patients had had their melanoma removed with an excisional biopsy with a small margin before scintigraphy. The site of these melanomas was the occipital region (Fig. 1), the helix of the right ear (Fig. 2) and the left arm (Fig. 3). In none of these three patients was metastatic tumor found on microscopic examination of the sentinel nodes.

DISCUSSION

The present study indicates that lymphoscintigraphy with ^{99m}Tc-nanocolloid for lymphatic mapping may not always reflect the complete drainage pattern. In 3 (12%) of 25 patients, the exact number of sentinel nodes could not be reproduced in a repeat study. Their melanomas were not located on the trunk. Mudun et al. (*22*) reported a 50% discordance in a similar study of six patients.

Because scintigraphy is a crucial part of lymphatic mapping, this apparent inconsistency needs to be examined and solved. Four possible explanations for the limited reproducibility may be considered.

TABLE 2
Clinical Characteristics and Lymphoscintigraphic and Surgical Data

Patient no.	Sex	Age (yr)	Primary site	No. of sentinel nodes		
				1st scan	2nd scan	Excised
1	M	44	Leg	1	1	1
2	M	67	Trunk	2	2	2
3	F	27	Leg	3	3	3
4	F	47	Leg	1	1	1
5	M	43	Trunk	3	3	4
6	M	36	Trunk	1	1	3
7	F	69	Leg	1	1	1
8	F	27	Leg	3	3	3
9	F	21	Arm	1	1	1
10	F	47	Arm	1	1	1
11	F	41	Trunk	2	2	1
12	F	49	Arm	2	1	1
13	M	56	Trunk	2	2	2
14	F	42	Head/Neck	2	3	2
15	F	64	Leg	2	2	2
16	F	48	Trunk	1	1	1
17	M	47	Leg	1	1	1
18	F	58	Leg	2	2	2
19	F	41	Leg	3	3	5
20	M	42	Arm	1	1	1
21	F	55	Head/Neck	2	1	2
22	M	35	Head/Neck	4	4	4
23	F	55	Leg	1	1	1
24	F	25	Trunk	1	1	1
25	M	57	Trunk	3	3	4

The radiopharmaceutical was administered to all patients in an identical manner around the tumor site. Two to four injections were given, depending on the length of the wound. The objective was to raise a wheal, a sign that the colloid was indeed injected intradermally. Morton et al. (*15*) stress the importance of using only a small volume (~0.5 ml) for intradermal injection because a larger dose tends to cause spread into deeper (subcutaneous) layers and different lymphatic ducts. Our doses have never exceeded a total volume of 0.35 ml. Although every effort was made to ensure that the sites of injection as well as the injected volume were identical in the first and second scans, small variations are inevitable. These

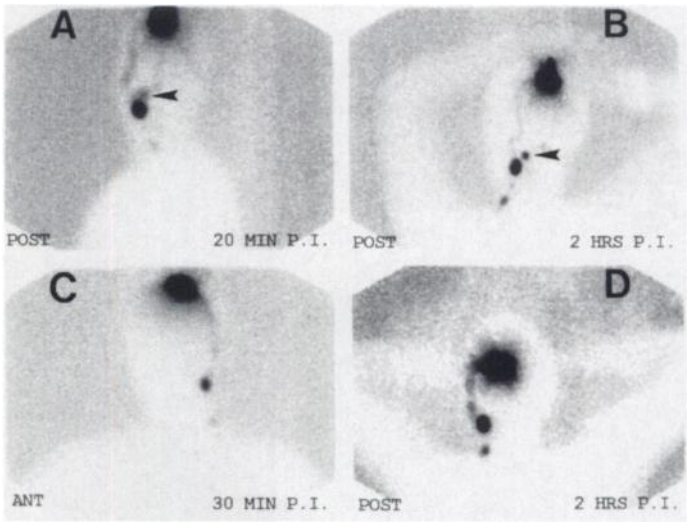

FIGURE 1. Scans from a 55-yr-old woman with a melanoma in the occipital region. The first series (A, B) shows drainage to two sentinel nodes (arrow) in the left posterior (POST) triangle of the neck. The second series (C, D) shows only one of these two nodes.

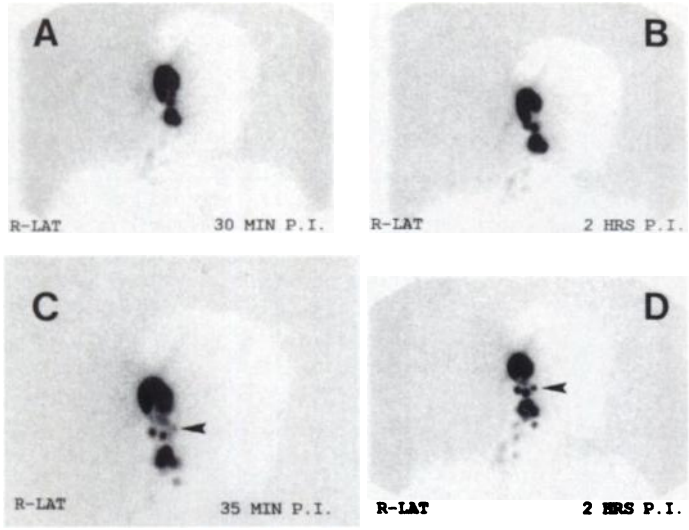

FIGURE 2. Scans from a 42-yr-old woman with a melanoma on the helix of the right ear. Two sentinel nodes in the right neck are depicted on the first series (A, B), whereas the second series (C, D) shows an additional third sentinel node (arrow). Multiple second-echelon nodes are visible in the lower part of the neck. R-LAT = right lateral; P.I. = postinjection.

variations may account for the different outcomes seen in these three patients.

The optimal particle size for lymphoscintigraphy for inert colloids is suggested to be on the order of tens of nanometers (*23*). The particle size of the ^{99m}Tc-nanocolloid that we used was less than 80 nm, with 77.1% less than 30 nm (*24*), which made this tracer particularly suitable for our purposes. Technetium-99m-nanocolloid is widely used in Europe but not in the United States. It has not yet been compared with other widely used tracers, such as ^{99m}Tc-antimony sulfide colloid, ^{99m}Tc-stannous phytate, ^{99m}Tc-antimony sulfide colloid and ^{99m}Tc-dextran. Further investigation of the agent and comparison with other tracers may be needed to exclude unfavorable characteristics that may explain our sometimes variable findings. Furthermore, it has been reported (*23*) that sulfur colloid particle size increases after approximately 5 hr. Changes like these, if occurring in ^{99m}Tc-nanocolloid, could influence the outcome of scans. We ensured that the ^{99m}Tc-nanocolloid had been drawn up shortly before injection.

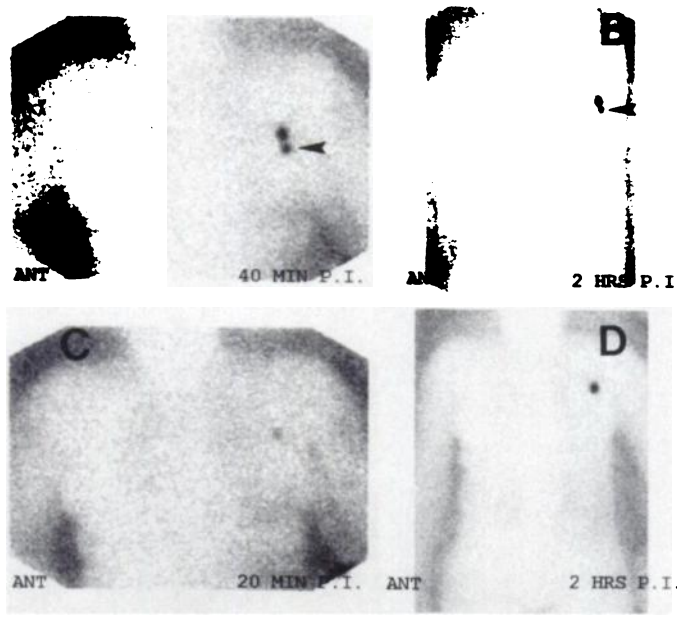

FIGURE 3. Scans from a 49-yr-old woman with a melanoma on the left arm. The first series (A, B) shows two sentinel nodes (arrow) in the left axilla, whereas on the second series (C, D) only one of these remains visible.

Anatomic studies by Sappey (*25*) and Haagensen (*26*) have demonstrated that the skin contains an intricate maze of lymph drainage ducts, all possibly leading to different nodes. Their observations led us to wonder whether lymphatic drainage may vary in time within an individual patient. Factors such as previous exertion, body hydration and variation in oncotic and hydrostatic pressure of the blood may play a role (*27*). Lymphoscintigraphy reflects drainage and will reflect such variability.

In most patients, the first scintigraphic study was done a few weeks after the primary lesion had been excised. All patients underwent their second preoperative scan a maximum of 4 wk after the first scan. It is well known that the process of wound healing takes many months. Because granulation tissue is gradually replaced by more dense and compact fibrous tissue, it is conceivable that such alterations influence to some extent the lymphatic drainage of the area concerned.

The finding that lymphoscintigraphy is not always reproducible may explain some of the false-negative sentinel node procedures. Results of more than 600 such operations have been described, with 1.3% false-negative results (*15,19,28–32*). Limited accuracy of lymphoscintigraphy means that in some patients sentinel nodes are not visualized. Some of these nodes will be discovered at operation by injection of blue dye at the site of the primary lesion (*15*), but others may remain undetected. Approximately 20% of these nodes will contain metastatic melanoma and may lead to false-negative sentinel node procedures.

What can be done to improve the results of lymphoscintigraphy? The technique of administration may be improved by injecting circumferentially around the primary lesion or along the entire length on each side of the biopsy scar. Also, a study comparing ^{99m}Tc-nanocolloid with other radiopharmaceuticals for optimal imaging of lymphatic drainage may be useful.

CONCLUSION

The reproducibility of lymphoscintigraphy using ^{99m}Tc-nanocolloid as the radiopharmaceutical is high, but not 100%. Surgeons should realize that an occasional sentinel node may go undetected. A number of options may be entertained, but no conclusive explanation can be given as to why some sentinel nodes are not depicted on some of the images. The issues raised in the present study may warrant further investigation.

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Does Bone SPECT Actually Have Lower Sensitivity for Detecting Vertebral Metastasis Than MRI?

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We compared the ability of bone SPECT and MRI to detect vertebral metastasis. **Methods:** Skeletal scintigraphy, including planar and SPECT imaging, and spinal MRI examinations, were performed in 22 cancer patients in whom a total of 88 metastatic foci and 12 degenerative joint disease lesions were detected. Metastatic foci were defined as lesions that suggested metastasis on MRI and/or bone destruction on radiographs or CT and/or aggravation of increased tracer uptakes on serial bone scans. Image reconstruction of axial, coronal and sagittal sections was processed in a 128 × 128 matrix. MRI studies were performed with a 1.5 tesla signal scanner using fast spin-echo sequences. T1- and T2-weighted images were obtained in the sagittal plane. **Results:** Twenty patients had at least one vertebral metastasis. MRI diagnosed 86 of the 88 (97.7%) metastatic foci; bone SPECT correctly diagnosed 81 of 88 (92.0%); and planar imaging detected 62 of 88 (70.4%). The two vertebrae with metastasis not detected by MRI were clearly seen by bone SPECT. Extra-vertebral body metastases (e.g., in the pedicle, lamina, transverse and spinous processes) were, however, most often detected by SPECT, followed by MRI and planar imaging (40 versus 32 versus 4). **Conclusion:** Vertebral SPECT, using high-resolution SPECT equipment, produced excellent results that were comparable to and complementary with MRI in detecting vertebral metastasis. Our data suggest that vertebral SPECT is superior to MRI in detecting extra-vertebral body metastasis.

Key Words: bone SPECT; MRI; vertebral metastasis

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Bone scintigraphy is the most common imaging technique for detecting osseous metastasis throughout the skeleton. The most frequently performed radionuclide study, in Japan alone it accounts for approximately 30% of the procedures performed by institutions specializing in nuclear medicine. There are, however, reports that skeletal scintigraphy is less effective than MRI in detecting vertebral metastasis (*1–9*). But in these studies, bone planar imaging, not bone SPECT imaging, was compared with MRI. SPECT has proven superior to planar imaging in detecting various bone diseases (*10–13*). Because no studies comparing them have been reported, it is not clear whether bone SPECT has a lower sensitivity than MRI in detecting focal vertebral metastasis. In view of the importance of the early detection of vertebral metastasis and our great interest in bone SPECT, we thought it of clinical value that such a comparison between the two tomographic modalities be made.

MATERIALS AND METHODS

We retrospectively reviewed skeletal scintigrams and MRI studies of the thoracolumbar spine. Both skeletal scintigraphies, including planar and SPECT imaging, and spinal MRI examinations were performed in 22 cancer patients who had complained of back pain. Their ages ranged from 18 to 80 yr (mean 61.1 yr). Histologically proven diagnoses were as follows: nine cases of breast carcinoma (all women), five of prostatic carcinoma (all men), and one each of pulmonary carcinoma (male), renal cell carcinoma (male), pancreatic carcinoma (male), Wilms' tumor (female), hepatocellular carcinoma (male) and adenocarcinoma of unknown primary site (male).

All patients were followed for at least 18 mo after skeletal scintigraphy and spinal MRI examination. The final diagnosis of vertebral or disk lesions was based on the results of all radiological studies, including repeated skeletal scintigraphies, MRI, computed tomographic (CT) scans, plain radiographs and the subsequent clinical course.

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