Kinetics of Three Lymphoscintigraphic Agents in Patients with Cutaneous Melanoma

Edwin C. Glass, Richard Essner and Donald L. Morton
Division of Surgical Oncology, Department of Nuclear Medicine, John Wayne Cancer Institute, Saint John's Health Center, Santa Monica, California

Although lymphoscintigraphy is commonly used for the preoperative evaluation of patients with cutaneous melanoma and for intraoperative identification of sentinel lymph nodes, there is no consensus regarding the most useful radiopharmaceuticals or imaging times. **Methods:** Fifty-one consecutive patients with clinical American Joint Committee on Cancer Stage I or II melanoma were assigned to one of three groups of 17 for lymphoscintigraphy with one of three radiopharmaceuticals: ^{99m}Tc-albumin colloid (AC), ^{99m}Tc-human serum albumin (HSA) or ^{99m}Tc-sulfur colloid (SC). Colloidal agents were filtered through 0.2 μm filters. After injecting 18.5–30 MBq (500–800 μCi) of the radiopharmaceutical, dynamic monitoring over injection sites and node basins was performed to identify draining lymphatic channels and sentinel nodes. In addition, static digital and analog images were acquired from the injection site and draining node basins immediately after injection and at 30 min (early) and 2 to 4 hr (delayed) after injection. Dynamic and static images were analyzed to determine transit times to the sentinel node, the number of nodes visualized in early and delayed images, the quality of lymph node and lymph channel visualization, the sentinel-to-nonsentinel uptake ratios and the washout rates from injection sites. **Results:** Early images with all three agents provided reliable identification of sentinel lymph nodes. Technetium-99m-HSA demonstrated faster washout rates from injection sites and better definition of lymph channels than either particulate agent, whereas particulate agents were retained longer in nodes and demonstrated more nodes in delayed images than in early images. All agents demonstrated lymph channels better in early images than in delayed images. In general, variations between patients exceeded differences between agents. Sentinel nodes could not be distinguished reliably from nonsentinel nodes in delayed images alone. **Conclusion:** All three agents are acceptable for cutaneous lymphoscintigraphy, but reliable identification of sentinel nodes and their afferent lymph channels requires early imaging. Delayed imaging or localization alone is unreliable and may lead to incorrect identification of the sentinel node.

Key Words: lymphoscintigraphy; melanoma; technetium-99m-sulfur colloid; technetium-99m-human serum albumin; technetium-99m-albumin colloid; sentinel lymphadenectomy

J Nucl Med 1998; 39:1185–1190

Since the introduction of cutaneous lymphoscintigraphy for identifying the draining lymph nodal basin by Morton et al. in 1977 (*1,2*), the method has become well established for identifying the draining nodal basin in cutaneous melanoma (*3,4*). Current interest in this procedure reflects the growing popularity of intraoperative lymphatic mapping with selective lymphadenectomy as a minimally invasive operative technique to determine the tumor status of the draining lymph node basins for a primary cutaneous melanoma (*5–11*). The accuracy of the intraoperative procedure depends in part on the accuracy of preoperative lymphoscintigraphy. In addition, radiopharmaceuticals are used increasingly for intraoperative use in localizing lymph nodes (*12–15*).

Numerous radiopharmaceuticals have been previously used for lymphoscintigraphy, including ^{99m}Tc-labeled dextran (*4*), ^{99m}Tc hydroxyethyl starch (*16*), ^{99m}Tc-human serum albumin (HSA) (*17–20*) and several labeled colloids (*21*), including ^{198}Au colloid (*2*), ^{99m}Tc stannous phytate (*22*), ^{99m}Tc-sulfur colloid (SC) (*21,23,24*), ^{99m}Tc antimony sulfur colloid (*21*) and preparations of ^{99m}Tc-albumin colloid (AC) (*25,26*). Among these agents only ^{99m}Tc-AC, ^{99m}Tc-HSA and ^{99m}Tc-SC are available presently as commercial products in the U.S.

There is still no consensus regarding the optimal methods for lymphoscintigraphy. The intralymphatic kinetics of presently available lymphoscintigraphic radiopharmaceuticals are not well understood. An improved understanding of the in vivo kinetics of these radiopharmaceuticals could lead to more accurate as well as more efficient procedures for lymphatic localization. This clinical investigation was done to evaluate and compare the in vivo kinetics and localization of three agents that have previously been used for lymphoscintigraphy and that are currently available through commercial sources in the U.S. The agents were studied in patients with cutaneous melanoma having routine preoperative lymphoscintigraphy.

MATERIALS AND METHODS

Between October 21, 1994 and November 10, 1995, 51 patients with clinical Stage I cutaneous melanoma who had cutaneous lymphoscintigraphy for preoperative nodal localization were studied. All patients had American Joint Committee on Cancer (AJCC) Stage I or II cutaneous melanoma of intermediate thickness, confirmed by incisional or excisional biopsy (<1.5-cm margins), and all were scheduled for wide excision of the primary site and regional lymphadenectomy after preoperative lymphoscintigraphy. None of the patients had undergone operative procedures that would disrupt or alter the pathway of lymphatic drainage. Patients were selected from the population of all patients having cutaneous lymphoscintigraphy on the basis of availability of technical personnel and the specific equipment used to record and analyze the data according to the methods detailed below. During the dates given above, the protocol for imaging was the same in patients included in this study and those not included. Only the computer recording and data analysis differed in the patients studied.

Patients randomly received one of three radiopharmaceuticals: ^{99m}Tc-AC (Microlite EI DuPont de Nemours, Billerica, MA), ^{99m}Tc-HSA (Amersham-Mediphysics, Arlington Heights, IL) or ^{99m}Tc-SC (Amersham-Mediphysics by CIS-US, Bedford, MA). All radiopharmaceuticals were prepared and stored according to the manufacturers' instructions. Details of these procedures are specified in the package inserts provided by the manufacturers. Technetium-99m used for labeling was commercially supplied (Mediphysics, Inc., Culver City, CA) as pre-eluted ^{99m}Tc-pertechnetate from generators after 4 to 24 hr of ingrowth. Technetium-99m-SC was prepared by adding ^{99m}Tc-pertechnetate and hydrochloric acid

Received Jun. 9, 1997; revision accepted Oct. 21, 1997.
For correspondence or reprints contact: Edwin C. Glass, MD, Department of Nuclear Medicine, Saint John's Health Center, 1328 Twenty-Second Street, Santa Monica, CA 90404.

solution to a vial containing sodium thiosulfate, followed by immersion of the vial for 5 min in a vigorously boiling water bath. The vial was allowed to cool at room temperature for 3 min before adding sodium biphosphate anhydrous and sodium hydroxide. The colloidal radiopharmaceuticals, ^{99m}Tc-AC and ^{99m}Tc-SC, were filtered through 0.2-micron filters (Nalgene®, Rochester, NY) before injection.

With meticulous attention to injection technique and special care to avoid subcutaneous placement of the needle 18.5–30 MBq (500–800 μCi) of radiopharmaceutical were injected intradermally. The radiopharmaceutical was injected at two to four sites surrounding or at the site of the primary melanoma. Each injection was performed so as to raise a wheal beneath or surrounding the site of the primary tumor. Injectate volumes ranged from 0.2–0.5 ml. Injections were individualized in consideration of local skin turgor and body location, such that identical volumes of injectate were not used in all patients. In each patient, however, it was determined at the time of injection that an adequate wheal was produced at the site of the injection(s) so as to reproduce in as realistic manner as possible the lymphatic drainage of the primary melanoma. No massage, external heat or other maneuvers were applied to the site of injection. After the injection was completed, continuous dynamic monitoring was performed over all potential node areas for identification of the draining basin(s), sentinel node(s) and their afferent lymph channel(s) until the sentinel node was identified. This monitoring was performed by continuous and repeated acquisitions on the image screen of the scintillation camera as well as by continuously observing the persistence scope of the camera until the sentinel node appeared. In addition, analog and digital imaging of both the injection site and the draining nodal basins was performed specifically at three times: immediately after injection; at 30 min (early); and from 2–4 hr (delayed) after injection. The time of the delayed images varied according to patient convenience and availability of the scintillation camera and computer. All images were acquired using a large field scintillation camera interfaced to a computer. Images were recorded on film and simultaneously in computer using 128 × 128 × 16 matrices. The injection site was imaged at all three time points. Patients were repositioned in precisely the same manner relative to the camera head and collimator face for all digital images of both injection sites and nodes.

The time between injection and first identification of the sentinel lymph node(s) was recorded as the transit time in minutes. The number of nodes visualized in the images was recorded for both the early and delayed images. The quality of visualization of nodes and their afferent channels was ranked on a scale of 0 (no visualization) to 5 (excellent visualization) at the time of lymphoscintigraphy, and the observer had no knowledge of the clinical outcome or radiopharmaceutical used. Both early and delayed images were ranked.

Washout rates from the injection site were calculated using regions of interest over the injection sites in the digital images acquired at the three time points: immediate, early and delayed. Half-time of washout was determined by a least-squares fit of a single exponential through these three points or data pairs (time, counting rate), with correction for the decay of ^{99m}Tc. Ratios of counting rates of the sentinel node (or hottest sentinel node if more than one sentinel node was present) and the next hottest node visualized were determined from the delayed images using standard software for region of interest analysis. Background subtraction was not used. The activity in the nodal basins was almost entirely confined to lymphatic structures (nodes and channels).

TABLE 1
Locations of Primary Melanomas and Injection Sites

	^{99m}Tc-AC (n = 17)	^{99m}Tc-HSA (n = 17)	^{99m}Tc-SC (n = 17)
Extremity	8	7	6
Trunk	8	6	9
Head and neck	1	4	2

AC = albumin colloid, filtered; HSA = human serum albumin; SC = sulfur colloid, filtered.

Statistical Methods

Two-tailed chi-square testing was used to test for differences between the groups of patients receiving different radiopharmaceuticals with regard to gender or location on the body of the primary melanoma. F-testing was used to test for differences between the groups of patients receiving different radiopharmaceuticals with regard to age. Kruskal-Wallis one-way analysis of variance on ranks was used to test for differences between radiopharmaceutical groups with regard to transit times, number of nodes demonstrated, quality of visualization of nodes, quality of visualization of channels, sentinel-to-nonsentinel uptake ratios and washout rates from sites of injection, with subsequent pairwise multiple comparisons by Dunnett's method when significant variances in ranks were observed. It also was used to test for differences in the number of nodes demonstrated as a function of the location of the primary melanoma. The non-normality of the distributions of these variables precluded standard analysis of variance and Student's t-testing. The two-tailed Wilcoxon matched-pairs, signed-rank test was used to study paired observations in patients at different times, i.e., observations of the number of nodes, the quality of visualization of nodes and the quality of visualization of lymphatic channels at early and delayed imaging times in the same patient. Differences were regarded as significant when p values were < 0.05. Pearson correlation coefficients were tested under the hypothesis that they did not differ from zero using the Student-t transformation, and p values < 0.05 were regarded as significant.

RESULTS

The study population included 20 women and 31 men. The average age was 55 ± 16 yr (mean ± s.d.). Kinetics of the three lymphoscintigraphic agents were evaluated in 17 patients each, or 51 patients total. There were no significant intergroup differences among radiopharmaceutical groups by patient gender ($p = 0.72$), by age ($p > 0.1$) or by the anatomic sites of the primary melanomas ($p = 0.686$) (Table 1).

Transit times from injection site to appearance in the sentinel node differed significantly between agents ($p = 0.015$). Technetium-99m-HSA demonstrated the sentinel nodes more quickly than the particulate agents (Fig. 1). Variations from patient to patient exceeded differences between agents. There was no significant correlation between age of the patient and arrival time to sentinel node ($r = 0.08$, $p > 0.05$).

The number of nodes demonstrated at either early or delayed imaging times did not differ significantly from agent to agent by Kruskal-Wallis testing ($p = 0.445$ and $p = 0.441$ at early and at delayed imaging times, respectively). An average of 2.17 ± 1.33, 2.23 ± 0.90 and 2.09 ± 1.94 (mean ± s.d.) nodes were demonstrated in early images and 2.82 ± 1.70, 2.65 ± 2.15 and 3.82 ± 3.11 nodes in delayed images for ^{99m}Tc-AC, ^{99m}Tc-HSA and ^{99m}Tc-SC, respectively (Fig. 2). Delayed images demonstrated wide a variation among individual patients in the number of nodes visualized (1–7 for ^{99m}Tc-AC, 0–9 for ^{99m}Tc-HSA and 1–14 for ^{99m}Tc-SC). The number of nodes

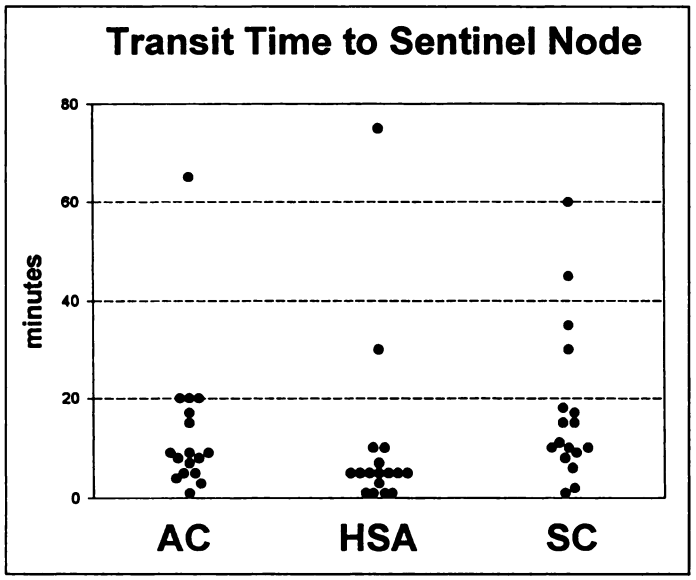

FIGURE 1. Interpatient variations in transit times from injection sites to sentinel nodes exceeded variations between particular agents. Technetium-99m-HSA demonstrated more consistent and slightly shorter arrival times to the sentinel nodes.

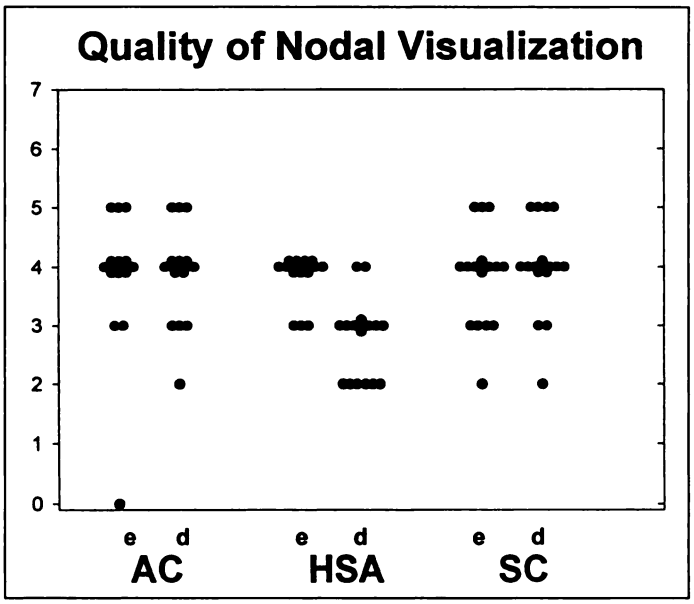

FIGURE 3. Nodal visualization was rated from 0 (no visualization) to 5 (excellent). Early images (e) were of similar quality with all three agents. Technetium-99m-HSA seemed to wash out from nodes by the time of delayed imaging, which was not observed with the particulate agents (^{99m}Tc-AC and ^{99m}Tc-SC).

demonstrated at 30 min was not found to vary with the location of the primary melanoma ($p = 0.480$) when classified as in Table 1.

In early images, the quality of nodal visualization did not differ among the three agents ($p = 0.736$) (Fig. 3), but lymph channels were visualized more clearly using ^{99m}Tc-HSA than either particulate agent ($p = 0.009$) (Fig. 4). In delayed images, both ^{99m}Tc-AC and ^{99m}Tc-SC demonstrated nodes more clearly than ^{99m}Tc-HSA ($p < 0.001$), with no significant differences between ^{99m}Tc-AC and ^{99m}Tc-SC ($p > 0.05$) (Fig. 3). Lymph channels were poorly visualized with all agents in delayed images (Fig. 4).

Half-times of washout from injection sites averaged 7.5 ± 6.4, 4.3 ± 1.4 and 13.9 ± 12.7 hr, respectively, for ^{99m}Tc-AC, ^{99m}Tc-HSA and ^{99m}Tc-SC (Fig. 5). These rates differed significantly ($p = 0.003$). Technetium-99m-HSA washed out more rapidly than either particulate agent. Washout rates also were more uniform from patient to patient with ^{99m}Tc-HSA than with the particulate agents (Fig. 5). No significant correlation was observed between half-times of washout and age of the patient ($r = -0.153$, $p > 0.05$).

Findings with the three agents were compared at early versus delayed imaging times. Both particulate agents (^{99m}Tc-AC and ^{99m}Tc-SC) demonstrated more nodes in delayed images than in early images (mean 2.8 versus 2.2 nodes for ^{99m}Tc-AC and 3.8 versus 2.1 nodes for ^{99m}Tc-SC) ($p < 0.02$ and < 0.003, respectively) (Fig. 2). Technetium-99m-HSA demonstrated an average of 2.6 versus 2.2 nodes in delayed versus early images, not a significant difference ($p = 0.625$). Lymph channels were

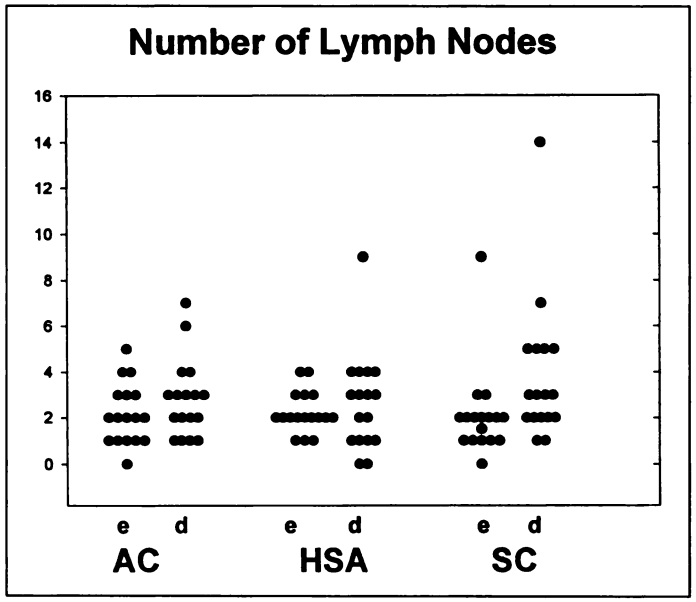

FIGURE 2. Comparison of number of nodes demonstrated in early (e) and delayed (d) images. Even at 30 min after injection (e), multiple nodes were frequently visualized. All three agents demonstrated similar numbers of nodes in early images. Delayed images showed more nodes than early images when the particulate agents (^{99m}Tc-AC and ^{99m}Tc-SC) were used.

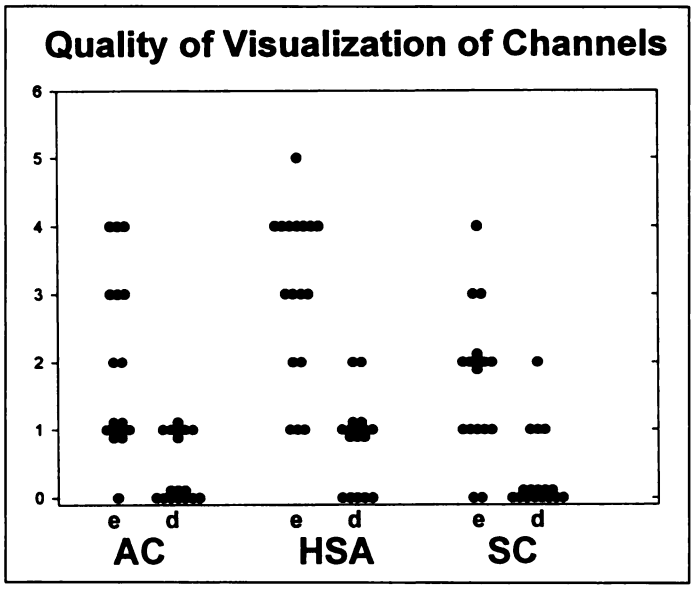

FIGURE 4. Afferent lymph channels leading to sentinel nodes were more clearly delineated in early images (e) than in delayed images (d) with all three agents. Delayed imaging proved unsatisfactory for the delineation of lymph channels.

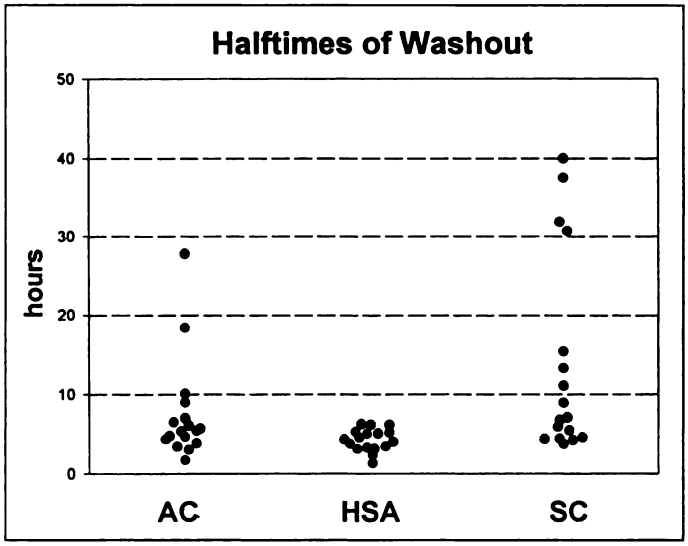

FIGURE 5. Half-times of washout of radiopharmaceuticals from injection sites. Technetium-99m-HSA demonstrated faster washout kinetics than the particulate agents (^{99m}Tc-AC and ^{99m}Tc-SC). This was associated with shorter arrival times to the sentinel nodes.

seen much more clearly in early images than in delayed images (Fig. 4) with all three agents.

In 28 of the 51 patients it was possible to calculate ratios of external counting rates of sentinel-to-nonsentinel nodes, using the next hottest nonsentinel node in delayed images. This ratio could not be determined in all 51 patients because 12 patients demonstrated only one node (10 patients) or no nodes (2 patients) in delayed images, and 11 patients had film but not digital images. Fourteen of 28 patients (50%) demonstrated uptake in sentinel nodes that was more than twice as great as the uptake in the next hottest node, but the other 14 did not demonstrate this gradient in uptake (Fig. 6). Including the 10 patients with only one node seen, as well as the 2 patients with no nodes seen in the delayed images, 24 of 40 (60%) had significant (>2:1) uptake ratios in delayed images, whereas 16 of 40 (40%) did not. Although the mean values of the uptake ratios differed for the three agents in the delayed images (3.83 ± 2.93, 1.54 ± 1.06 and 3.52 ± 2.95 (mean ± s.d.) for

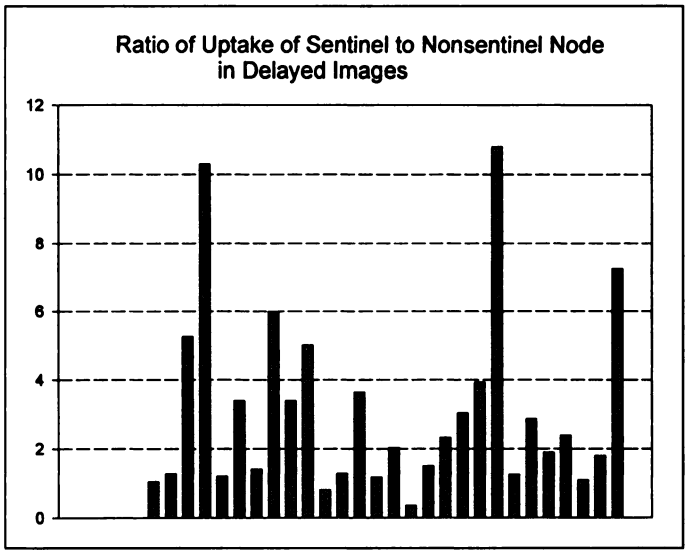

FIGURE 6. Sentinel-to-nonsentinel radioactivity ratios at 2–4 hr after injection in 28 patients who demonstrated at least two nodes. This ratio was > 2:1 in only 14 of 28. If delayed uptake alone is used for imaging or for probe localization, the possibilities of misidentification or overidentification of the sentinel node are apparent.

^{99m}Tc-AC, ^{99m}Tc-HSA and ^{99m}Tc-SC, respectively), differences in these ratios were not significant by Kruskal-Wallis testing ($p = 0.124$).

DISCUSSION

Selective lymphadectomy is evolving as a rational and effort-effective approach to managing patients with clinical Stage I melanoma (*8,11,13*). The development of effective adjuvant therapy with alpha interferon for patients with spread to regional lymph nodes (*27*) has further increased the need for effective methods to identify relevant lymph nodes for clinical staging. Removal of a limited number of the most relevant nodes allows more detailed and accurate analysis of these nodes (*28*). The adoption of these methods into routine clinical management of patients has motivated the collection of data in this study.

Most of the radiopharmaceuticals previously reported as useful for lymphatic imaging are not widely available at present. For example, previous investigations have revealed that ^{99m}Tc antimony trisulfide colloid, ^{198}Au colloid and ^{99m}Tc albumin nanocolloid, all of which feature small particle sizes, are useful agents for nodal localization (*21,26*). None of these is commercially available in the U.S. We therefore evaluated the properties of three agents available in the U.S.: ^{99m}Tc-AC, ^{99m}Tc-HSA and ^{99m}Tc-SC, all of which feature the advantages of a ^{99m}Tc label. Because particle size affects lymphatic transit (*21,24,25,29*), the particulate agents, ^{99m}Tc-AC and ^{99m}Tc-SC, were filtered through submicron filters before injection (*13,14,24,25*). Lymphatic flow also is affected by local hyperthermia (*30*) and massage applied to the site of injection (*13,29,30*). These maneuvers were not used in this study, because we were evaluating the properties of the native radiopharmaceuticals.

All three agents provided useful lymphoscintigrams of good quality, but they exhibited different imaging properties. Technetium-99m-HSA demonstrated slightly faster kinetics than the particulate agents. This was evidenced both by shorter arrival times and by faster washout from the sites of injection. These observations are in agreement with those reported by Lamki et al. (*17*). Technetium-99m-HSA also was somewhat more predictable in its rate of flow and washout. These characteristics of ^{99m}Tc-HSA could allow faster procedures for either preoperative or intraoperative nodal localization, provided that the interval between injection and localization is relatively brief. Particulate agents demonstrated more nodal retention as measured by qualitative scoring of nodal visualization and by the greater number of nodes visualized in delayed versus early images. These comparative properties of the particulate and nonparticulate agents would support efforts to develop new radiopharmaceuticals that confer the relative advantages of both types of agents (*31*).

The localization of tracer in lymph nodes was time-dependent. Waiting even half an hour after injection usually resulted in the uptake of tracer by multiple nodes, with even more nodes appearing as sentinel nodes by 2 to 4 hr after injection (Figs. 2 and 7). These findings are in agreement with those of Taylor et al. (*32*) and others who have emphasized the importance of immediate and early imaging or probe localization if the first or sentinel node is to be identified reliably (*9,15,33*). These data suggest that preoperative injection followed by intraoperative localization with a probe alone may increase the risk of identifying the wrong node, removing more nodes than necessary, and/or missing sentinel nodes and basins. The mere presence of radioactivity in a node does not ensure that it is a sentinel node. We also observed two patients who demonstrated

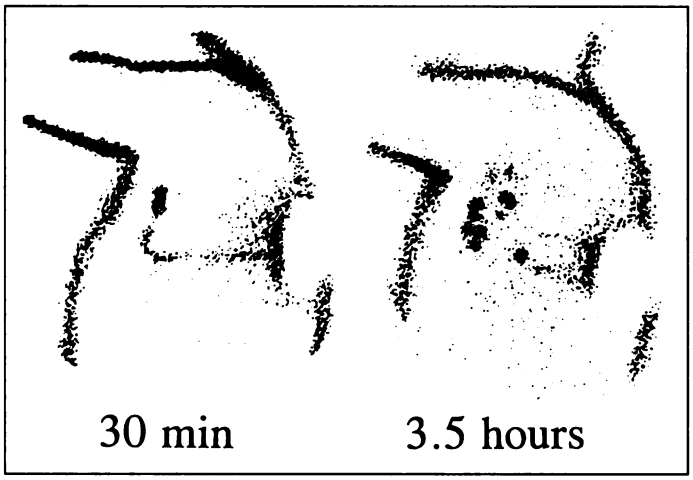

FIGURE 7. Demonstration of variation between early and delayed nodal uptake. This figure illustrates the dynamic behavior of radiocolloid (^{99m}Tc-SC) in a patient with a primary melanoma behind left scapula. The early image (left) demonstrates both afferent lymphatic channel and sentinel node. In the delayed image (right), from the same injection, the afferent lymphatic channel is no longer delineated, and tracer has migrated to several axillary nodes, obscuring identification of the sentinel node.

nodes in early images but no nodes in delayed images using ^{99m}Tc-HSA. Body location was not found to be a significant determinant of the number of nodes at 30 min by statistical testing, although anatomical considerations are important when considering the number of nodes to anticipate. For example, we frequently observe dual sentinel nodes in the groin, and metastases to popliteal nodes also may be encountered from melanomas of the lower leg.

Both preoperative lymphoscintigraphy and the intraoperative use of blue dye (*8*) could avert these potential difficulties. The intraoperative use of blue dye provides a critical visual aid for nodal identification. Preoperative injections followed by lymphoscintigraphy with a large field gamma camera allow accurate identification of nodal basins, afferent lymphatic channels (*4–7,9,32,34*) and sentinel nodes. Preoperatively marking the location of the sentinel nodes with ink marks on the skin, using the gamma camera and probe, greatly facilitates the operative approach to the appropriate lymph nodes, with intraoperative visual confirmation by blue dye. We currently perform preoperative localization using both the scintillation camera and an external probe in the nuclear medicine department.

If the afferent channel can be located using blue dye, it can be tracked to the sentinel node (*8*). These channels are readily identified and localized by lymphoscintigraphy, but early imaging is required (Figs. 4 and 7). Immediate dynamic imaging after injection, with application of ink marks on the skin overlying the channels, is optimal for their preoperative localization. We found that all three agents permitted reliable localization of channels in early but not in delayed images.

With time, tracer cleared from lymphatic channels and moved into additional nodes, and this was more noticeable with the particulate agents. This phenomenon confers an advantage in terms of greater overall nodal uptake but confounds preoperative detection of channels and identification of sentinel versus nonsentinel lymph nodes (*15,32,33*). For intraoperative use, longer delays after injection have been claimed to result in increasing uptake of tracer in the sentinel node (*13*). Although this undoubtedly occurs in some patients, when we measured the relative activities in sentinel versus nonsentinel nodes in delayed images, we observed either no sentinel uptake or uptake ratios < 2:1 in 40% of delayed images. Similarly, Kapteijn et al. (*15*) reported an overlap in the counting rates of sentinel and nonsentinel nodes. In our measurements, the nodes within the same basin were located at similar depths beneath the skin and similar distances from the collimator. This implies that differences in attenuation had little influence on these observations, and suggests that similar gradients should be encountered using an intraoperative probe. Uptake ratios < 2:1 or < 3:1 could result in the misidentification of the sentinel node or result in the identification and removal of excessive numbers of nodes using a hand-held probe. On the other hand, to the extent that delayed migration of tracer compounds predicts the migration of tumor cells, the identification of additional nonsentinel nodes may be of clinical significance. We included ratios from patients studied with all agents. A more extensive study with larger numbers of patients studied with any agent might yield slightly different results, but inspection of Figure 2 reveals that satellite nonsentinel localization occurred with all the agents assessed. Although we observed a tendency for higher uptake ratios with particulate tracers in delayed images, statistically significant differences in uptake ratios between agents were not demonstrated in the small number of patients in whom the uptake ratios were determined.

Although some physicians have used injections up to 24 hr before localization (*12,15*), we did not image patients beyond 4 hr after injection because it was not clinically practical. Comparative evaluation of imaging at such delayed times will require further studies with regard to kinetics, nodal retention of radiopharmaceuticals and the number of nodes visualized. Finally, because our data were obtained from intradermal injections in patients with cutaneous melanoma, the findings may have little or no relationship to lymph node localization procedures in patients with breast cancer (*35–38*). Our results might also have been different if maneuvers to increase lymph flow had been used (*13,29,30*), or if filtration of the colloidal agents had been accomplished differently or not used at all.

The relatively slow washout from the injection site of the particulate radiopharmaceuticals is associated with a protracted local deposition of energy. Using the assumptions of distribution in four grams of tissue, complete absorption of low-energy gamma emissions, Auger electrons, conversion electrons and low-energy x-rays, and assuming 1.6% absorption of the principal 140-keV photons of ^{99m}Tc (*39*), local doses at the injection site in the skin can be estimated for each of the radiopharmaceuticals based on their mean half-times of washout. This yields estimates of 1.4, 1.1 and 1.8 cGy/MBq (52, 40 and 66 rads/mCi) for ^{99m}Tc-AC, ^{99m}Tc-HSA and ^{99m}Tc-SC, respectively. Dispersion of the dose in tissue, incomplete local absorption of emissions, nonexponential washout and other influences would mitigate these estimates of local exposures. These localized doses would be comparable to or less than doses that result from partial infiltrations of significantly greater quantities of ^{99m}Tc commonly used for other diagnostic studies. After lymphoscintigraphy, patients in this study had wide excision of the sites of the primary melanomas and, therefore, local radiation at injection sites was of little clinical relevance.

CONCLUSION

Accurate localization of sentinel nodes was demonstrated using each of the three radiopharmaceuticals. Timing after injection was an important determinant of localization in both nodes and lymphatic channels for all tracers studied. Early images are necessary for the identification of lymphatic channels. Particulate agents gave somewhat more prolonged retention in nodes, but nonparticulate ^{99m}Tc-HSA demonstrated slightly more rapid localization in a consistent manner. Although it is appealing from a practical standpoint, delayed

imaging alone is not suitable for identifying sentinel nodes in cutaneous melanoma.

ACKNOWLEDGMENTS

This work was supported in part by Grants CA12582 and CA29605 from the National Cancer Institute and by funding from the Wrather Family Foundation (Los Angeles) and the Steele Foundation (Phoenix). Richard Essner is the recipient of an American Cancer Society Development Award.

REFERENCES

1. Holmes EC, Moseley HS, Morton DL, Clark W, Robinson D, Urist MM. A rational approach to the surgical management of melanoma. *Ann Surg* 1977;186:481–490.
2. Fee HJ, Robinson DS, Sample WF, Graham LS, Holmes EC, Morton DL. The determination of lymph shed by colloidal gold scanning in patients with malignant melanoma: a preliminary study. *Surgery* 1978;84:626–632.
3. Sullivan DC, Croker BP, Harris CC, Deery P, Seigler HF. Lymphoscintigraphy in malignant melanoma: ^{99m}Tc antimony sulfur colloid. *Am J Roentgenol* 1981;137:847–851.
4. Bennett LR, Lago G. Cutaneous lymphoscintigraphy in malignant melanoma. *Semin Nucl Med* 1983;13:61–69.
5. Lock-Andersen J, Rossing N, Drzewiecki KT. Preoperative cutaneous lymphoscintigraphy in malignant melanoma. *Cancer* 1989;63:77–82.
6. Norman J, Cruse CW, Espinosa C, et al. Redefinition of cutaneous lymphatic drainage with the use of lymphoscintigraphy for malignant melanoma. *Am J Surg* 1991;162:432–437.
7. Berman CG, Norman J, Cruse CW, Reintgen DS, Clark RA. Lymphoscintigraphy in malignant melanoma. *Ann Plast Surg* 1992;28:29–32.
8. Morton DL, Duan-Ren W, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;127:392–399.
9. Uren RF, Howman-Giles RB, Shaw HM, Thompson JF, McCarthy WH. Lymphoscintigraphy in high risk melanoma of the trunk: predicting drainage node groups, defining lymphatic channels, and locating the sentinel node. *J Nucl Med* 1993;34:1435–1440.
10. Ross MI, Reintgen D, Balch CM. Selective lymphadenectomy: emerging role for lymphatic mapping and sentinel node biopsy in the management of early stage melanoma. *Semin Surg Oncol* 1993;9:219–223.
11. Essner RE. The role of lymphoscintigraphy and sentinel node mapping in assessing patient risk in melanoma. *Semin Oncol* 1997;24:S4–8–S4–10.
12. Krag DN, Sybren JM, Weaver DL, et al. Minimal-access surgery for staging malignant melanoma. *Arch Surg* 1995;130:654–658.
13. Albertini JJ, Cruse CW, Rapaport D, et al. Intraoperative radiolymphoscintigraphy improves sentinel node identification for patients with melanoma. *Ann Surg* 1996;223:217–224.
14. Mudun A, Murray DR, Herda SC, et al. Early stage melanoma: lymphoscintigraphy, reproducibility of sentinel node detection, and effectiveness of the intraoperative gamma probe. *Radiology* 1996;199:177–175.
15. Kapteijn BAE, Nieweg OE, Muller SH, et al. Validation of gamma probe detection of the sentinel node in melanoma. *J Nucl Med* 1997;38:362–366.
16. Sadek S, Owunwanne A, Abdel-Dayem HM, Yacoub T. Preparation and evaluation of ^{99m}Tc-99m hydroxy-ethyl starch as a potential radiopharmaceutical for lymphoscintigraphy: comparison with ^{99m}Tc human serum albumin, ^{99m}Tc dextran, and ^{99m}Tc sulfur microcolloid. *Lymphology* 1989;22:157–166.
17. Lamki LM, Haynie TP, Balch CM, Bhadkamkar VA, Podoloff DA, Kim EE. Lymphoscintigraphy in the surgical management of patients with truncal melanoma: comparison of technetium sulfur colloid with technetium human serum albumin [Abstract]. *J Nucl Med* 1989;30:844.
18. McNeill GC, Witte MH, Witte CL, et al. Whole-body lymphoscintigraphy: preferred method for initial assessment of the peripheral lymphatic system. *Radiology* 1989;172:495–502.
19. Kataoka M, Kawamura M, Hamada K, Itoh H, Nishiyama Y, Hamamoto K. Quantitative lymphoscintigraphy using ^{99m}Tc human serum albumin in patients with previously treated uterine cancer. *Br J Radiology* 1991;64:1119–1121.
20. Esato K, Ohara M, Seyama A, et al. Technetium-99m HSA lymphoscintigraphy and leg edema after arterial reconstruction. *J Cardiovasc Surg* 1991;32:741–746.
21. Strand S-E, Persson RBR. Quantitative lymphoscintigraphy I: basic concepts for optimal uptake of radiocolloids in the parasternal lymph nodes of rabbits. *J Nucl Med* 1979;20:1038–1046.
22. Alavi A, Staum MM, Shesol BF, Bloch PH. Technetium-99m stannous phytate as an imaging agent for lymph nodes. *J Nucl Med* 1978;19:422–426.
23. Persson RBR, Naversten Y. Technetium-99m sulfide colloid preparation for scintigraphy of the reticuloendothelial system. *Acta Radiology Ther Phys Biol* 1970;9:567–576.
24. Hung JC, Wiseman GA, Wahner HW, Mullan BP, Taggart TR, Dunn WL. Filtered technetium-99m sulfur colloid evaluated for lymphoscintigraphy. *J Nucl Med* 1995;36:1895–1901.
25. Saha GP, Feiglin DHI, O'Donnell JK, Go RT, Karam PM, MacIntyre W. Experience with technetium-99m albumin colloid kit for reticuloendothelial system imaging. *J Nucl Med Technol* 1986;14:149–151.
26. Pijpers R, Collet GJ, Meijer S, Hoekstra OS. The impact of dynamic lymphoscintigraphy and gamma probe guidance on sentinel node biopsy in melanoma. *Eur J Nucl Med* 1995;22:1238–1241.
27. Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 1996;14:7–17.
28. Cochran AJ, Wen D-R, Morton DL. Occult tumor cells in the lymph nodes of patients with pathological stage I malignant melanoma. *Am J Surg Pathol* 1988;12:612–618.
29. Ikomi F, Hanna GK, Schmidt-Schonbein GW. Mechanism of colloid uptake into the lymphatic system: basic study with percutaneous lymphography. *Radiology* 1995;196:107–113.
30. Avery M, Nathanson SD, Hetzel FW. Lymph flow from murine foot pad tumors before and after sublethal hyperthermia. *Radiation Res* 1992;132:50–53.
31. Vera DR, Wisner ER, Stadalnik RC. Sentinel node binding via a nonparticulate receptor-binding radiotracer. *J Nucl Med* 1997;38:530–535.
32. Taylor A, Murray D, Herda S, Vansant J, Alazraki N. Dynamic lymphoscintigraphy to identify the sentinel and satellite nodes. *Clin Nucl Med* 1996;21:755–758.
33. McCarthy WH, Thompson JF, Uren RF. Invited commentary. *Arch Surg* 1995;130:569–660.
34. Norman J, Kruse W, Ruas E, et al. The expanding role of lymphoscintigraphy in the management of cutaneous melanoma. *Am Surg* 1989;55:689–694.
35. Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg* 1995;222:394–401.
36. Uren RF, Howman-Giles RB, Thompson JF, et al. Mammary lymphoscintigraphy in breast cancer. *J Nucl Med* 1995;36:1775–1780.
37. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996;276:1818–1822.
38. Pijpers R, Meijer S, Hoekstra OS, et al. Impact of lymphoscintigraphy on sentinel node identification with technetium-99m-colloidal albumin in breast cancer. *J Nucl Med* 1997;38:366–368.
39. Zanzonico PB, Brill AB, Becker DV. Radiation dosimetry. In: Wagner HN, Szabo Z, Buchanan JW, eds. *Principles of nuclear medicine*. Philadelphia: WB Saunders Company; 1995:107–134.