INVITED COMMENTARY

Reproducibility of Cutaneous Lymphoscintigraphy: Same or Different Lymphatic Routes and Sentinel Nodes After Reinjection?

Almost 10 y after the clinical introduction of the sentinel node procedure for cutaneous melanoma (*1*), both the diagnostic and the prognostic accuracy of the method are now well established. By combining preoperative lymphoscintigraphy with intraoperative γ probe and blue dye–assisted detection, one can detect the sentinel node in nearly all patients (*2–4*). A 30-patient learning phase appears to be sufficient to obtain a detection rate of virtually 100% (*3*). At The Netherlands Cancer Institute, the evaluation of the results of the first 200 melanoma patients who underwent a sentinel node biopsy from 1993 showed a 3-y overall survival rate of 93% if the sentinel node was tumor negative and 67% if the sentinel node was tumor positive (*4*). Other investigators have also shown the prognostic value of the tumor status of the sentinel node (*5*).

Preoperative cutaneous lymphoscintigraphy appears to be an important first step in lymphatic mapping for sentinel lymphadenectomy. It serves five purposes: to point out the draining lymph node field at risk for metastatic disease, to indicate the number of sentinel nodes, to help distinguish first-tier nodes from secondary nodes, to detect sentinel nodes in unpredictable locations, and to mark the location of the sentinel node on the skin. With an interobserver agreement of more than 98% (*6*), cutaneous lymphoscintigraphy is particularly useful for lymphatic mapping of sites, such as the head, neck, and trunk, in which lymphatic flow to more than a single adjacent predictable nodal group may vary from 40% to 75% (*7,8*). At these sites, lymphoscintigraphy did extend the predicted area of ambiguous lymphatic drainage from primary axial melanomas to 11 cm on either side of the midline or above and below Sappey's line (the gently curved line drawn on skin between a point 2 cm above the umbilicus and the level of the second lumbar vertebra on the back) instead of the usual limit of 2.5 cm from these lines when anatomic guidelines are followed (*9*). This ability to reliably identify drainage routes enables lymphoscintigraphy to predict more than 98% of the basins that contain lymph node metastases (*10*).

Against this background of large individual variability in lymphatic drainage, the assessment of reproducibility of cutaneous lymphoscintigraphy for sentinel node detection is of great importance. A lack of reproducibility may increase false-negative rates and the risk of melanoma recurrence. In the study presented by Rettenbacher et al. (*11*) in this issue of *The Journal of Nuclear Medicine*, a reproducibility of 84% on the basis of 100 patients was found. In 59 of these patients, the primary tumor was on the trunk, head, or neck. These findings are concordant with reproducibilities of 85% and 88% found for cutaneous lymphoscintigraphy in 1996 in two smaller series of patients (*12,13*). The finding that lymphoscintigraphy is not always reproducible may be explained by small differences in injection technique or in the variation of tracer particle composition. Also, patient-related factors such as previous exertion, body hydration, and variation in oncotic and hydrostatic pressure of blood may play a role (*14*). Finally, the time interval after excision of the melanoma may be important because granulation tissue is gradually replaced by more dense and compact fibrous tissue in the process of wound healing. In the two previous reproducibility studies, the time interval for reinjection varied from 2 d to 4 wk, and similar injection site–to–tumor distances for both lymphoscintigraphy examinations were taken. In the study of Rettenbacher et al., reinjection was performed the day after the first lymphoscintigraphy examination, with margins of 10 mm from the tumor site instead of the 2–5 mm used for the first injection. The trend in management of melanoma is toward narrower diagnostic excisions, and a margin of 2 mm is currently recommended (*15*). Despite going against this trend, this article provides interesting data that deserve comment. Expanding the margins for injection caused the sentinel node visualization rate to increase from 93% (by narrow injection margins) to 100%, including visualization of all sentinel nodes previously detected by the first lymphoscintigraphy examination. Further, additional sentinel nodes were displayed in 16 patients. In 2 of them, an additional basin was found in the contralateral axilla, and in 1, in the ipsilateral groin. An important question arises from these findings: Is the

Received Sep. 13, 2000; revision accepted Sep. 29, 2000.

For correspondence or reprints contact: Renato A. Valdés Olmos, MD, PhD, Department of Nuclear Medicine, The Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam, 1066 CX, The Netherlands.

more distant injection more accurate? As stated by the authors, it might be. On the other hand, expanding the injection distance from the site of the primary tumor may increase the ambiguous zone of drainage, cross a lymphatic watershed, and visualize additional basins not really related to drainage of the tumor site. Further, a 93% sentinel node identification rate with injection closer to the biopsy scar is low compared with what other investigators have reported (*2–4*). These aspects and the fact that none of the additional sentinel lymph nodes was found to contain metastases lead to some caution in considering the more distant injection as a new standard. Its application as yet would be recommended to nuclear medicine physicians, and also to surgeons with respect to the use of blue dye, only in patients with scar hypertrophy or inflammation after excisional biopsy or in patients with no visualization after standard injection technique.

Another important aspect of the study of Rettenbacher et al. (*11*) concerns the 76% concordance found for lymph channel visualization between both injection techniques. This rate is clearly lower than the concordance found for sentinel nodes and draining lymphatic basins. It can be concluded that, although expansion of tracer injection margins activates different lymph channels for drainage in one of every four patients, in only a few patients is this accompanied by additional draining sentinel nodes and basins, and never at the expense of the originally identified routes. This certainty that, despite the existence of various Caesars and many ways, all routes eventually lead to Rome, can be of assistance only for the definitive confirmation of lymphoscintigraphy as an essential test for preoperative lymphatic mapping in cutaneous melanoma. It confirms also that the best strategy to detect the sentinel node rests on the combination of scintigraphy, γ probe, and blue dye.

Renato A. Valdés Olmos
Omgo E. Nieweg
The Netherlands Cancer Institute
Amsterdam, The Netherlands

REFERENCES

1. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg.* 1992;127:392–399.
2. Pijpers R, Borgstein PJ, Meijer S, Hoekstra OS, van Hattum LH, Teule GL. Sentinel node biopsy in melanoma patients: dynamic lymphoscintigraphy followed by intraoperative gamma probe and vital dye guidance. *World J Surg.* 1997;21:788–792.
3. Morton DL, Thompson JF, Essner R, et al., for the Multicenter Selective Lymphadenectomy Trial Group. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. *Ann Surg.* 1999;230:453–463.
4. Jansen L, Nieweg OE, Peterse JL, Hoefnagel CA, Valdés Olmos RA, Kroon BBR. Reliability of sentinel lymph node biopsy for staging melanoma. *Br J Surg.* 2000;87:484–489.
5. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol*. 1999;17:976–983.
6. Uren RF, Howman-Giles RB, Shaw HM, Thompson JF, McCarthy WH. Lymphoscintigraphy in high-risk melanoma of the trunk: predicting draining node groups, defining lymphatic channels and locating the sentinel node. *J Nucl Med.* 1993;34:1435–1440.
7. Bennet LR, Lago G. Cutaneous lymphoscintigraphy in malignant melanoma. *Semin Nucl Med*. 1983;13:61–69.
8. Everbach MA, Wahl RL, Argenta LC, Froelich J, Niederhuber JE. Utility of lymphoscintigraphy in directing surgical therapy for melanomas of the head, neck and upper thorax. *Surgery*. 1987;102:433–442.
9. Norman J, Cruse W, Espinosa C, et al. Redefinition of cutaneous lymphatic drainage with the use of lymphoscintigraphy for malignant melanoma. *Am J Surg.* 1991;162:432–437.
10. Berger DH, Feig BW, Podoloff D, et al. Lymphoscintigraphy as a predictor of lymphatic drainage from cutaneous melanoma. *Ann Surg Oncol*. 1997;4:247–251.
11. Rettenbacher L, Koller J, Kässmann H, Holzmannhofer J, Rettenbacher T, Galvan G. Reproducibility of lymphoscintigraphy in cutaneous melanoma: can we accurately detect the sentinel lymph node by expanding the tracer injection distance from the tumor site? *J Nucl Med*. 2001;42:424–429.
12. Kapteijn BAE, Nieweg OE, Valdés Olmos RA, et al. Reproducibility of lymphoscintigraphy for lymphatic mapping in cutaneous melanoma. *J Nucl Med*. 1996;37:972–975.
13. Mudum 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;199:171–175.
14. Wahl RL, Geatti O, Liebert M, Wilson B, Shrewe P, Beers BA. Kinetics of interstitially administered monoclonal antibodies for purposes of lymphoscintigraphy. *J Nucl Med.* 1987:28:1736–1744.
15. Kroon BBR, Nieweg OE, Hoekstra HJ, Lejeune FJ. Principles and guidelines for surgeons: management of cutaneous malignant melanoma. *Eur J Surg Oncol.* 1998;23:550–558.