PAPER

Interval Sentinel Lymph Nodes in Melanoma

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Hypothesis: For patients with melanoma, interval or in-transit sentinel lymph nodes (SLNs) have the same risk for nodal metastasis as SLN in traditional (ie, cervical, axillary, and inguinal) nodal basins.

Design: Prospective clinical trial.

Setting: Multicenter study.

Patients: Eligible patients were aged 18 to 70 years with melanomas of at least 1.0-mm Breslow thickness and nodes with clinically negative findings.

Intervention: Sentinel lymph node biopsy was guided by preoperative lymphoscintigraphy to identify all SLNs.

Main Outcome Measures: We evaluated interval nodal sites, including epitrochlear, popliteal, and subcutaneous or intramuscular nodes outside of traditional basins, for the presence of metastases.

Results: The SLNs were identified in 2332 nodal basins from 2000 patients. In 62 patients (3.1%), interval SLNs were identified. We found SLN metastases in 442 (19.5%) of 2270 conventional nodal basins and 13 (21.0%) of 62 interval sites. In 11 (84.6%) of the 13 cases in which we found an interval node that was positive for metastatic disease, it was the only site of nodal metastasis.

Conclusions: Although interval SLNs are identified infrequently, they contain metastatic disease at nearly the same frequency as SLNs in cervical, axillary, and inguinal nodal basins. Positive interval SLNs are likely to be the only site of nodal metastasis. Therefore, detailed preoperative lymphoscintigraphy and meticulous intraoperative search for interval nodes should be performed.

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SENTINEL LYMPH node (SLN) biopsy has become widely accepted as a method of staging the regional lymph nodes of patients with melanoma.[1-5] The presence of positive metastatic disease in a sentinel node is the single most important prognostic factor predicting survival.[6] High-risk patients with metastatic disease in the SLN are appropriate candidates for therapeutic completion lymphadenectomy and adjuvant therapy. Although the value of early therapeutic lymph node dissection and early institution of adjuvant therapy remains controversial, the available evidence suggests that early treatment of microscopic nodal metastases is preferable to waiting for the development of palpable nodal disease.[7]

Sentinel lymph node biopsy is performed by injection of radioactive colloid and a vital blue dye, which travel through the afferent lymph channels to identify the first-draining, or sentinel, node. Preoperative lymphoscintigraphy, a nuclear medicine scan, is performed routinely to identify the location of the SLN.[8,9] Previous studies have demonstrated that lymphatic drainage patterns are not always accurately predicted on anatomic grounds, especially for melanomas of the trunk or of the head and neck.[10-14] Although most melanomas exhibit lymphatic drainage to conventional nodal basins (ie, the cervical, axillary, and inguinal nodes), some patients have drainage to lymph nodes outside of these basins.[15-25] Variously termed *interval*, *in-transit*, *ectopic*, or *intercalated nodes*, these lymph nodes outside the conventional nodal basins sometimes contain metastatic disease and may be the only site of nodal metastasis. The present analysis was performed to determine the frequency with which interval nodes are identified and the incidence of nodal metastasis.

PATIENTS AND METHODS

The Sunbelt Melanoma Trial is a multicenter, prospective, randomized study involving 79 centers across the United States.[26] Patients enrolled from June 1, 1997, through July 31, 2001, were included in this analysis. The study was approved by the institutional review boards of the participating institutions. Eligibility criteria included patients aged 18 to 70 years with cutaneous melanomas of at least 1.0-mm Breslow thickness and clinically negative (nonpalpable) regional lymph nodes.

After informed consent was obtained, patients underwent wide local excision of the primary melanoma and SLN biopsy using intradermal injection of isosulfan blue dye and technetium Tc 99m (^{99m}Tc) sulfur colloid around the site of the primary tumor. Preoperative lymphoscintigraphy was performed to identify all draining nodal basins and interval sentinel nodes. A handheld gamma probe was used intraoperatively with visualization of blue dye to guide SLN detection. The protocol specified that all blue nodes, and all nodes with a level of radioactivity of at least 10% of the most radioactive or "hottest" node should be removed and designated SLNs.

All sentinel nodes underwent histological analysis with hematoxylin-eosin (H&E) staining at multiple levels, followed by immunohistochemistry (IHC) for S100 protein. Sentinel nodes were divided into blocks based on lymph node size; at least 5 sections per block were evaluated by means of H&E staining and 2 sections per block by means of IHC. In addition, IHC staining for HMB-45 or MART-1 was performed selectively at a few institutions. The primary melanoma and SLN pathologic features from the first 10 cases from each institution and all cases of an SLN positive for metastatic disease were reviewed by a central pathology review committee. A positive SLN was defined as having histological evidence of metastasis or IHC-detected foci of cells that could be confirmed as malignant by means of either H&E staining or nuclear morphology.

Patients found to have an SLN with metastatic disease on results of H&E staining and/or IHC underwent completion dissection of the lymph nodes of the involved nodal basin(s). Nonsentinel nodes were evaluated by means of routine H&E staining (not serial sectioning or IHC). Conventional nodal basins were considered to be the cervical (including parotid), axillary, and inguinal nodes. Nodes outside these basins were considered interval, in-transit, or ectopic nodes. Patients included in this analysis underwent successful biopsy of the SLN identified by preoperative lymphoscintigraphy. The SLN identification rate for all patients included in the study was 99.7%. Statistical comparison was performed using Fisher's exact test. Significance was determined at $P<.05$.

Table 1. Clinicopathologic Features of Patient Population

Factor	% of Patients* (N = 2000)
Breslow thickness, mm	
≤2	63.6
>2-4	24.9
>4	10.1
Unknown	1.5
Clark level	
II	2.2
III	22.0
IV	68.1
V	3.6
Unknown	4.1
Ulceration	
Absent	70.6
Present	26.2
Unknown	3.1
Histological subtype	
Superficial spreading	47.8
Nodular	28.7
Lentigo maligna melanoma	1.2
Acral lentiginous	2.6
Not otherwise specified	15.9
Unknown	3.9
Regression	
Absent	79.5
Present	9.4
Unknown	11.1

*Due to rounding percentages in each category may not total 100.

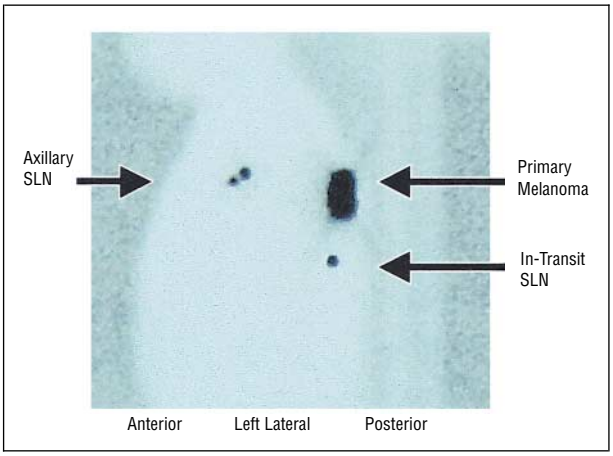

Figure 1. Lymphoscintigram of a patient with a primary melanoma in the left scapular region, demonstrating axillary nodal drainage and an interval sentinel lymph node (SLN) in the subcutaneous tissues of the back.

RESULTS

The SLNs were identified in 2332 nodal basins from 2000 patients. In 62 patients (3.1%), interval SLNs were identified. The 64 interval nodal sites represented 2.7% of all nodal basins. The distribution of interval nodal sites by site of the primary melanoma is shown in **Table 1**. **Figure 1** and **Figure 2** illustrate examples of interval nodal drainage seen on lymphoscintigraphy.

For melanomas of the upper extremity, epitrochlear nodes represented the interval site in 15 of 16 cases. For melanomas of the lower extremity, the interval nodes were found in the popliteal area in 8 of 9 cases. For head and neck melanomas, interval nodes were found in the occipital and postauricular/mastoid areas in 12 of 15 cases. Interval nodes for truncal melanomas were most frequently found in the subcutaneous tissues of the back and flank.

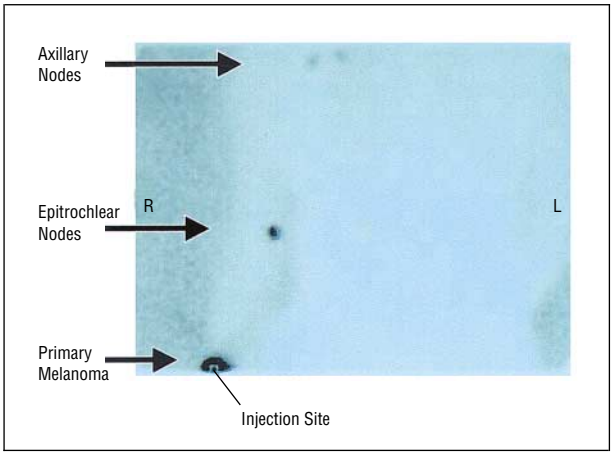

Figure 2. Lymphoscintigram of the anterior chest, arm, and elbow area of a patient with a primary melanoma of the wrist, with intense uptake of radioactive colloid in an epitrochlear node and fainter uptake of tracer in the axillary nodes. In such cases, it can be difficult to determine whether the epitrochlear node is the true sentinel node and the axillary nodes are second-echelon nodes, or whether separate lymph channels drain directly past the epitrochlear node to the axillary nodes. Therefore, radioactive nodes were harvested from each location. Blue dye uptake seen in the epitrochlear node but not in the axillary nodes suggests that the axillary nodes were second-echelon nodes. In this case, blue dye was found in the epitrochlear and axillary nodes. R indicates right; L, left.

Table 2. Frequency of Interval SLN by Site of the Primary Tumor*

Primary Tumor Site	No. of Patients	No. (%) of Patients With In-Transit SLNs
Upper extremity	423	16 (3.8)
Lower extremity	457	9 (2.0)
Trunk	901	24 (2.7)
Head and neck	219	15 (6.8)
Total	**2000**	**64** (3.2)

*SLN indicates sentinel lymph node.

Table 3. Comparison of Nodal Metastasis in Conventional Nodal Basins vs Interval Nodes*

Primary Tumor Site	Total Positive SLNs in Conventional Nodal Basins/Total Conventional Nodal Basins	Positive Interval SLNs/Total Interval Nodal Sites
Upper extremity	68/425 (16.0)	1/16 (6.0)
Lower extremity	100/463 (21.6)	2/9 (22.2)
Trunk	243/1149 (21.1)	5/24 (20.8)
Head and neck	31/233 (13.3)	5/15 (33.3)†
Total	**442/2270** (19.5)	**13/64** (20.3)

*Positive indicates sentinel lymph nodes (SLNs) as nodes with histological evidence of metastasis or immunohistochemistry-detected foci of cells that could be confirmed as malignant by means of hematoxylin-eosin staining or nuclear shape; conventional node basins, cervical, axillary, and inguinal. Data are given as number (percentage).
†$P<.05$ vs conventional nodal basins, Fisher exact test.

The SLN metastases were found in 442 (19.5%) of 2270 of conventional nodal basins, and 13 (20.3%) of 64 interval sites. In 11 (84.6%) of 13 cases in which we found an interval node positive for metastatic disease, it was the only site of nodal metastasis. The frequency of nodal metastasis in the interval nodes is shown in **Table 2**. Overall, the rate of metastasis in interval SLN was not different than that for conventional nodal basins (**Table 3**). For patients with melanomas of the head and neck, interval SLNs were more likely to contain metastatic disease than were SLNs in the expected cervical nodes. In each of the 5 cases of interval SLNs for head and neck melanomas positive for tumor, the nodes were located in the occipital or postauricular/mastoid areas, and these were the only positive SLNs.

COMMENT

In the present study, interval SLNs were identified in 3.1% of patients with melanoma. Overall, 13 (0.6%) of 2000 patients had interval nodes that contained metastatic disease. Most often, when an interval SLN was positive for tumor, it was the only site of nodal metastasis. Although this represents a very small proportion of the patient population, the implications of a positive interval SLN are the same as those of positive SLN in other sites. Specifically, patients with positive SLN are at higher risk for recurrence and death due to melanoma and may benefit from lymph node dissection and adjuvant therapy.[6,7] Therefore, drainage to interval nodes is an infrequent but important event that has significant implications for patient treatment.

Interval nodes can be identified reliably only by detailed preoperative lymphoscintigraphy and the intraoperative use of a handheld gamma probe. The use of blue dye as a single agent for lymphatic mapping and SLN biopsy in patients with melanoma, therefore, is not recommended, as this technique would not allow reliable identification of these nodes.

The 3.1% rate of interval nodal sites is somewhat lower than that seen in other studies. Uren et al[23] reported that interval nodes were identified in 7.8% of patients. Roozendaal et al[24] reported identification of interval nodes in 4.7%. In a study from Leong et al,[25] 5.8% of patients had nodal drainage to sites that could be classified as interval nodes. The lower incidence of interval SLNs in the present study may be related to several factors. First, different radioactive colloid agents used for lymphoscintigraphy may have greater sensitivity for identification of interval nodes. Uren et al[23] used ^{99m}Tc-labeled antimony trisulfide colloid, a very-small-particle colloid that may have advantages for interval node detection. Roozendaal et al[24] used ^{99m}Tc-labeled human albumin. In the present study and in that of Leong et al,[25] ^{99m}Tc sulfur colloid was used, which has relatively larger particles compared with the other agents. Another potential factor may be that the present study represents a broad multi-institutional experience from 79 centers, whereas the other studies were from single institutions with extensive experience in lymphoscintigraphy and SLN techniques. As pointed out by Uren et al,[23] high-quality lymphoscintigraphy requires specific high-resolution collimators for optimal gamma-camera imaging, with detailed imaging protocols. Variations in expertise, equipment, and imaging protocols among multiple centers may

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result in failure to identify interval SLNs in some cases. We could not, however, identify any significant variability among institutions in the identification of interval nodal sites, perhaps because of the large number of institutions involved in the study.

Specific patterns of interval nodal drainage have been reported. For melanomas of the distal extremity, epitrochlear or popliteal SLNs are found in a small fraction of patients. For melanomas of the trunk, drainage to lymph nodes in the triangular intermuscular space and other subcutaneous sites in the back and flank is not uncommon.[18] Drainage of truncal melanomas to interval nodes on the lateral chest wall just inferior to the axilla is a familiar pattern.[23,27]

Sentinel lymph node biopsy offers special challenges for melanomas in the head and neck. Scalp melanomas commonly drain to SLNs in the occipital or postauricular/mastoid areas, which can easily be missed or mistaken for cervical nodes without detailed, multiple-view lymphoscintigraphy that shows the relationship of the SLN to the sternocleidomastoid muscle and the ears.[10-12,28] These findings must be taken into account when deciding how to drape the sterile field to have access to these areas. In fact, the incidence of SLN metastases was higher for interval sites than for the expected cervical nodal basins in patients with melanomas of the head and neck. In all 5 cases of head and neck melanomas in which interval SLNs were positive for metastatic disease, the nodes were located in the occipital or postauricular/mastoid areas, and in all 5 patients, these were the only positive SLNs. Because of the unpredictable drainage of head and neck (especially scalp) melanomas, special care should be taken to ensure that all SLNs are removed for evaluation of metastatic disease. Although some might consider occipital or postauricular/mastoid nodal sites part of the cervical nodal chain, these nodes are not routinely removed in most standard neck dissections and can be easily overlooked.

We recommend that, even if the lymphoscintigram shows drainage to only interval nodal sites, intraoperative gamma-probe evaluation of the conventional regional node basin(s) should be performed, as occasionally the lymphoscintigram might miss less intense, but clinically important, radioactive uptake in regional nodes. In most cases, interval SLNs coexist with SLNs in cervical, axillary, or inguinal nodal basins. Although it may be difficult to discriminate true sentinel nodes from second-echelon nodes in this setting, "hot spots" (or radioactive uptake) seen on lymphoscintigraphy in a conventional basin concomitantly with an interval site (as in Figure 2) should be removed.

Another important surgical issue concerns nodal metastasis found at interval sites. Although available data to guide our decisions in this regard are scarce, we believe that it is appropriate to consider further surgical therapy for positive interval nodes in specific circumstances. Similar to lymph node dissection for conventional nodal basins, a positive finding for tumor in an SLN probably also indicates an increased risk for metastatic disease in the regional nonsentinel nodes.[29] Although lymphadenectomy of epitrochlear and popliteal nodes is not commonly performed, it should be considered if SLN metastasis is identified in these areas.[30] For isolated interval nodes in other areas, further dissection may not be feasible or necessary. Therefore, SLN biopsy alone seems to be adequate surgical therapy for such isolated interval nodes, even when metastatic disease is identified. However, if there is evidence of extracapsular nodal extension or any suspicion of contamination of the surgical wound with melanoma cells during excision of the node, reexcision of the interval site should be performed.

For patients with positive SLNs at interval sites, the question also arises as to what should be done about the

conventional nodal basin. For example, should an axillary dissection be performed for a positive SLN in the epitrochlear area with a negative finding in the SLN in the axilla? If a positive epitrochlear SLN is removed, but no drainage axillary SLN was seen on the lymphoscintigram, should axillary dissection be performed? We believe that the SLN procedure should guide the need for regional lymphadenectomy. That is, if no positive axillary SLN are present in these cases, axillary lymph node dissection is not required.

CONCLUSIONS

Although interval SLN are identified infrequently, they contain metastatic disease at the same frequency as SLN in cervical, axillary, and inguinal nodal basins. A positive finding of an interval SLN is likely to be the only site of nodal metastasis. Therefore, detailed preoperative lymphoscintigraphy and meticulous intraoperative search for interval nodes should be performed.

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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. Reintgen D, Cruse CW, Wells K, et al. The orderly progression of melanoma nodal metastases. *Ann Surg.* 1994;220:759-767.
3. Albertini, JJ, Cruse CW, Rapaport D, et al. Intraoperative radio-lymphoscintigraphy improves sentinel lymph node identification for patients with melanoma. *Ann Surg.* 1996;223:217-224.
4. Cascinelli N, Belli F, Santinami M, et al. Sentinel lymph node biopsy in cutaneous melanoma: the WHO Melanoma Program Experience. *Ann Surg Oncol.* 2000; 7:469-474.
5. Clary BM, Brady MS, Lewis JL, Coit DG. Sentinel lymph node biopsy in the management of patients with primary cutaneous melanoma: review of a large single-institutional experience with an emphasis on recurrence. *Ann Surg.* 2001;233: 250-258.
6. 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.
7. McMasters KM, Reintgen D, Ross MI, et al. Sentinel lymph node biopsy for melanoma: controversy despite widespread agreement. *J Clin Oncol.* 2001;19:2851-2855.
8. Uren RF, Howman-Giles RB, Thompson JF, et al. Lymphoscintigraphy to identify sentinel nodes in patients with melanoma. *Melanoma Res.* 1994;4:395-399.
9. Alazraki NP, Eshima D, Eshima LA, et al. Lymphoscintigraphy, the sentinel node concept, and the intraoperative gamma probe in melanoma, breast cancer, and other potential cancers. *Semin Nucl Med.* 1997;27:55-67.
10. Wells KE, Cruse CW, Daniels S, et al. The use of lymphoscintigraphy in melanoma of the head and neck. *Plast Reconstr Surg.* 1994;93:757-761.
11. O'Brien CJ, Uren RF, Thompson JF, et al. Prediction of potential metastatic sites in cutaneous head and neck melanoma using lymphoscintigraphy. *Am J Surg.* 1995;170:461-466.
12. Wanebo HJ, Harpole D, Teates CD. Radionuclide lymphoscintigraphy with technetium 99m antimony sulfide colloid to identify lymphatic drainage of cutaneous melanoma at ambiguous sites in the head and neck and trunk. *Cancer.* 1985; 55:1403-1413.
13. Uren DF, 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.
14. 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.
15. Thompson JF, Hunt JA, Culjak G, Uren RF, Howman-Giles R, Harman CR. Popliteal lymph node metastasis from primary cutaneous melanoma. *Eur J Surg Oncol.* 2000;26:172-176.
16. Hunt JA, Thompson JF, Uren RF, Howman-Riles R, Harman CR. Epitrochlear lymph nodes as a site of melanoma metastasis. *Ann Surg Oncol.* 1998;5:248-252.
17. Uren RF, Howman-Giles RB, Thompson JF, Shaw HM, McCarthy WH. Lymphatic drainage from peri-umbilical skin to internal mammary nodes. *Clin Nucl Med.* 1995;20:254-255.
18. Uren RF, Howman-Giles R, Thompson JF, et al. Lymphatic drainage to triangular intermuscular space lymph nodes in melanoma on the back. *J Nucl Med.* 1996; 37:964-966.
19. Uren RF, Howman-Giles R, Thompson JF. Lymphatic drainage of the skin of the back to retroperitoneal and paravertebral lymph nodes in melanoma patients. *Ann Surg Oncol.* 1998;5:384-387.
20. Uren RF, Thompson JF, Howman-Giles RB. Failure to detect drainage to popliteal and epitrochlear lymph nodes on cutaneous lymphoscintigraphy in melanoma patients [letter]. *J Nucl Med.* 1998;39:2195.
21. Thompson JF, Uren RF, Shaw HM, et al. The location of sentinel lymph nodes in patients with cutaneous melanoma: new insights into lymphatic anatomy. *J Am Coll Surg.* 1999;189:195-206.
22. Acca B, Kapteijn E, Nieweg OE, et al. Reproducibility of lymphoscintigraphy for lymphatic mapping in cutaneous melanoma. *J Nucl Med.* 1996;37:972-975.
23. Uren RF, Howman-Giles R, Thompson JF, et al. Interval nodes: the forgotten sentinel nodes in patients with melanoma. *Arch Surg.* 2000;135:1168-1172.
24. Roozendaal GK, de Vries JDH, van Poll D, et al. Sentinel nodes outside lymph node basins in patients with melanoma. *Br J Surg.* 2001;88:305-308.
25. Leong SPL, Achtem TA, Habib FA, et al. Discordancy between clinical predictions vs lymphoscintigraphic and intraoperative mapping of sentinel lymph node drainage of primary melanoma. *Arch Dermatol.* 1999;135:1472-1476.
26. McMasters KM, Sondak VK, Lotze MT, Ross MI. Recent advances in melanoma staging and therapy. *Ann Surg Oncol.* 1999;6:467-475.
27. Thelmo MC, Morita ET, Tresler PA, et al. Micrometastasis to in-transit lymph nodes from extremity and truncal malignant melanoma. *Ann Surg Oncol.* 2001;8:444-448.
28. Morton DL, Wen DR, Foshag LJ, Essner R, Cochran A. Intraoperative lymphatic mapping and selective cervical lymphadenectomy for early-stage melanoma of the head and neck. *J Clin Oncol.* 1993;11:1751-1756.
29. McMasters KM, Edwards MJ, Ross MI, et al, for the Sunbelt Melanoma Trial. Frequency of non–sentinel lymph node metastasis in melanoma. *Ann Surg Oncol.* In press.
30. Tanabe KK. Lymphatic mapping and epitrochlear lymph node dissection for melanoma. *Surgery.* 1997;121:102-104.

DISCUSSION

James E. Goodnight, Jr, MD, PhD, Sacramento, Calif: Dr McMasters and the Sunbelt Melanoma Trial Group have done pioneering work on the prognostic significance and standards of practice for SLN biopsy in patients with malignant melanoma. With this report, they add to our understanding of this elusive disease and further establish that SLN mapping and biopsy is a first-class technique for determining the regional extent of a primary melanoma. It is the best means we have for lymph node staging in this disease. At the very least, SLN biopsy should be part of standard staging procedures for any protocol study of primary melanoma, and I believe it to be a highly useful clinical tool. Moreover, Dr McMaster's demonstration that in-transit nodes in rare instances can be the sentinel draining lymph node firmly establishes the need for radioactive colloid mapping when one is performing SLN biopsy for melanoma. Blue dye alone is not enough.

Multiple excellent reports spanning the last decade demonstrate the efficacy of this technique. These studies notwithstanding, I still wonder at the improbability of a consistent first-draining lymph node for each part of the body and that the tumor status of that lymph node will accurately predict the tumor status of the regional lymph node basin. With all due respect to an outstanding contributor to surgical oncology and my mentor, Dr Donald Morton seemed to me to be selling us a used

car when he first presented his material a little more than a decade ago. So much for those of us of small mind and limited vision, and so it is that converts become missionaries. I am presently an SLN junkie, often to the chagrin of my colleagues. Dr McMasters et al have added to the fun by supporting the efficacy of hunting for in-transit SLNs.

There remain the overriding questions of whether lymph node dissection for patients with positive SLNs favorably affects their survival. To be sure, patients with stage III melanoma disease are cured, and presumably finding the disease early helps. In addition, depending on how one views interferon alfa-2b, when will we have an efficacious systemic adjuvant therapy? Dr McMasters voices these questions in a paper recently published.

Dr McMasters' study raises other wonderful, titillating questions, some of which I will articulate.

When you find a positive epitrochlear SLN, for example, or one in the auscultatory triangle on the upper back, do you perform a lymph node dissection or, maybe better stated, a reexcision of the area? I was surprised to learn that there is a published description of epitrochlear lymph node dissection.

Perhaps a more important question would be the example of a case of a lower-leg melanoma with a positive popliteal SLN and no obvious SLN in the groin. Would you dissect both the popliteal fossa and the groin?

Because I know he feels strongly about the issue, I will ask Dr McMasters whether in the case of a 1.5-mm-thick melanoma on the forearm and an epitrochlear lymph node showing a small focus of melanoma by immunohistochemistry only, and no other findings, would he refer that patient for adjuvant interferon alfa-2b?

David S. Robinson, MD, Kansas City, Mo: I, too, want to congratulate the authors on a very fine paper. My question is similar to that of Dr Goodnight. When you find an in-transit sentinel node containing metastatic disease and yet you find that the major basin to which it drains does not have a positive metastatic SLN (even when you can identify an SLN in that basin), do you resect that nodal basin knowing that the disease has a metastatic potential, or do you simply leave that basin alone?

Gerard V. Aranha, MD, Maywood, Ill: I enjoyed the paper, too, Dr McMasters, because I have come across the same problems, but my question to you is more technical. At the present time, there is a worldwide shortage of isosulfan blue and we have gone back to using methylene blue, which Dr Don Morton used in his first studies. We are finding that if you inject methylene blue intradermally, you can cause the skin to ulcerate and break down. So we are in our breast cases using intraparenchymal injections and for melanoma, subdermal injections. Have you had the same experience, and how would you handle that?

Richard C. Thirlby, MD, Seattle, Wash: I have 2 questions. Were the in-transit nodes blue? The second question relates to the pre–sentinel node literature, which was pretty convincing that there was no role for prophylactic node dissection in patients with thick melanomas (>3.5 or 4 mm). In your study, you include patients with thick melanomas. The explanation given for the lack of efficacy was the "cow is out of the barn," with systemic disease; hence, a node dissection would have no survival effect. I guess I don't see why that should change. Even if the node dissection is positive in those patients, their survival probably is not going to be affected by node dissection, so why are we doing sentinel nodes in thick-melanoma patients?

Dr McMasters: Dr Goodnight asked what to do when the epitrochlear node is positive. Should we do a lymph node dissection of the epitrochlear nodal basin? I too sought long and hard to find the description of doing an epitrochlear lymph node dissection and have done it on 1 or 2 occasions, although it is really controversial as to whether this is helpful or not. In the Sunbelt Melanoma Trial, we have made it optional to either do reexcision or lymph node dissection in these in-transit sites, because we simply don't know whether it is necessary. But, for popliteal and epitrochlear nodal basins with positive sentinel nodes, the other lymph nodes are at risk for metastatic disease. We have seen patients with poorly controlled local disease at those sites, so it may be reasonable to do further dissection. Certainly, if patients have, at in-transit sites, any concern that there was extracapsular extension or contamination of the wound when the node was excised, it is best to reexcise that site.

I was also asked about what to do about lower-leg melanoma with a positive popliteal sentinel node but no positive node in the groin. The question is, "Should we dissect the inguinal nodes?" This question has been brought up a couple of different ways. Again, not based upon an enormous amount of data, but our present practice and what we recommend is that we trust the SLN procedure. Unless a positive sentinel node is found in a nodal basin, we do not perform lymph node dissection. So if a sentinel node shows up on lymphoscintigram in the popliteal area, but nothing in the groin, we would carefully search intraoperatively using the gamma probe for any uptake in the groin area as well. If we did not find a positive sentinel node in the groin but we found one in the popliteal area, we would not do a groin dissection. The same thing holds true in the epitrochlear area and the axilla. If we don't find sentinel nodes that contain metastatic disease, we would not recommend doing a lymph node dissection in that nodal basin.

I was also asked about what to do with a 1.5-mm melanoma of the forearm with an epitrochlear node that is only positive by immunohistochemistry—whether to use interferon. One of the reasons why we are running the Sunbelt Melanoma Trial is in order to figure out what to do with these patients with very early nodal metastasis in a single SLN, and these patients are being randomized in this study to either receive interferon or get no adjuvant therapy whatsoever. So we hope that we will be able to answer that question in the coming years.

Dr Robinson also asked about a positive in-transit sentinel node and no positive SLN in the conventional nodal basin. Again, we trust the SLN result.

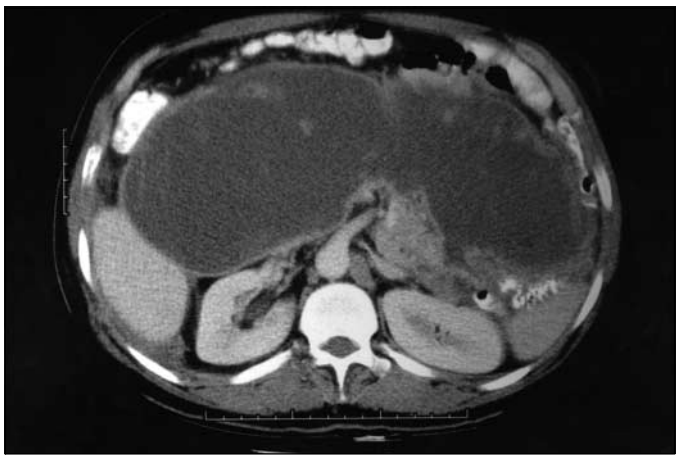
We were also asked about the isosulfan blue shortage, which has been a real problem nationwide. I have hoarded every vial of isosulfan blue dye I can get ahold of, but many people have had to use methylene blue—which does have those inherent problems of ulceration of the skin when injected intradermally. I believe that we found a solution to this problem just very recently. Isosulfan blue dye is a chemical compound that is available to be formulated by compounding pharmacies around the country, and these pharmacies just figured this out. But in our city and apparently in many other places around the country, you can contact one of these compounding pharmacies, basically give a verbal order every time you have a case—it's like giving a prescription—and they can mix a vial of this blue dye for you that is a generic compound of the same blue dye that we usually use. We have used it. It's the same exact thing and it works very well. I think that you should look into this at your institutions.

I was also asked if most of the nodes were blue that were in-transit nodes, and that is a good question. I don't know the answer. My personal experience is that most of the time when we find in-transit sentinel nodes, they are blue, but we did not evaluate that in this study and that is something we can look at.

The other philosophical question was whether or not we should do sentinel node biopsy for patients with melanomas that are 4 mm or greater in thickness. The conventional wisdom has been that patients who have thick primary melanomas greater than 4 mm don't benefit from regional node dissection because they have such a high risk of systemic metastasis. This has been the dogma for many years. However, that statement is not based upon any prospective randomized trials. In

fact, all of the prospective randomized trials looking at elective lymph node dissection excluded thick primary melanoma patients. There are some very interesting data now from institutions like M. D. Anderson and other places where they have looked at sentinel node biopsy for patients with thick primary melanomas. The 5-year survival rate from the M. D. Anderson series is 85% for thick primary melanoma patients who had negative sentinel nodes. Of course, if you have a positive SLN, the prognosis is much worse at about a 35% or 40% 5-year survival rate. But it's possible to identify a group of patients with thick primary melanomas who have a relatively much better prognosis and for whom additional therapy may really not be needed. We hope that with more sophisticated means of staging the regional lymph nodes and using reverse transcriptase polymerase chain reaction analysis and other methods, we may be able to weed out the good-prognosis patients and find those who are obviously very high risk. But that is a topic that deserves further study, and we are doing that in the Sunbelt Trial. I firmly believe, though, that there are some patients who have positive sentinel nodes, even though their melanoma is 4 mm thick, that will benefit from early removal of nodal metastasis as opposed to waiting until they develop bulky palpable nodal disease, and we recommend that those patients with positive sentinel nodes then undergo a therapeutic lymph node dissection. This is not now an elective lymph node dissection, but a therapeutic lymph node dissection, because the patients have been identified as having positive nodes and the other nodes in that nodal basin are at risk for disease.

Correction



Error in Figure Orientation. On the February 2002 cover of *Archives of Surgery*, the computed tomographic scan was positioned incorrectly. The spinal cord should have appeared at the bottom of the image, as shown here. The ARCHIVES regrets the error.