Hypothesis: Completion lymph node dissection (CLND) has usually been recommended after metastatic disease is identified in the sentinel lymph node (SLN) biopsy to eradicate further metastases in nonsentinel nodes. We hypothesized that patients with negative lymph nodes included in the initial SLN specimen have low risk of metastases in the residual draining basin and may not require CLND.

Design: Chart review.

Setting: University-affiliated tertiary care referral center.


Intervention: The SLN biopsy identified 87 patients (17.2%) with metastatic melanoma, of whom 80 underwent CLND.

Results: In 28 patients, all SLNs were found to contain metastatic melanoma. Seven (25%) of these patients had additional metastases identified in the CLND specimen. In 52 patients, 1 or more SLNs did not contain metastatic melanoma. Five (10%) of these patients had additional metastases in the CLND specimen ($P = .02$).

Conclusions: Although no evidence of metastatic melanoma was found on CLND in most patients in whom negative nodes had been removed with positive SLNs at the initial biopsy, 10% of these patients did have further metastases. This subgroup of patients (positive SLNs and negative nodes in the SLN biopsy specimen) is at significantly lower risk for further metastasis, but CLND cannot be safely omitted even for these patients.

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The incidence of melanoma in the United States has been increasing more rapidly than that of any other cancer during the past few decades. The lifetime risk of developing melanoma in 1960 was 1 in 600 individuals; it is currently approximately 1 in 70 individuals; and it is projected to be 1 in 50 individuals by 2010. It is the most deadly form of skin cancer and currently the eighth most common cancer in the United States. Moreover, melanoma affects young persons who are in the most productive years of their lives; accordingly, it constitutes a major public health problem.

Primary treatment of cutaneous melanoma has always included wide local excision, but the assessment and management of regional nodes has remained controversial. Clearly, regional lymph node metastasis in patients with primary cutaneous melanoma is the most important prognostic factor for tumor recurrence and survival. Its presence decreases the 5-year survival of these patients by approximately 40%, independent of, and superseding, any primary tumor characteristics. Thus, it was incorporated into the new American Joint Committee on Cancer staging system for cutaneous melanoma. The logical goal, therefore, has been to develop therapeutic strategies that would remove involved lymph nodes early in the course of the disease. Until recently, one such approach included elective lymph node dissection (ELND) for patients with high-risk primary lesions. Despite the theoretical benefits of this procedure, prospective trials have failed to confirm a survival advantage for the patients randomized to ELND except for perhaps selected subgroups. Obviously, this results from the inclusion, in the ELND group, of all high-risk patients, most of whom do not have positive nodes and therefore could not have benefited from regional node dissection.

The introduction and validation of sentinel lymph node (SLN) mapping and
biopsy during the past decade now permits identification of a subgroup of patients with metastatic disease with minimal morbidity. This technique has gained wide acceptance since the first report by Morton and colleagues in 1992, in particular since SLN results in significantly less morbidity than ELND and also identifies unsuspected draining nodal basins with the aid of lymphoscintigraphy.

Completion lymph node dissection (CLND) is recommended for the approximately 20% of patients with metastatic disease identified in sentinel nodes, based on the apparent benefit provided to this subgroup compared with delayed lymph node dissection at the time that clinical metastases are identified. As a result, SLN biopsy has evolved as the accepted regional nodes staging method, ELND has become a concept of historical interest, and approximately 80% of patients with high-risk primary lesions are spared the morbidity associated with ELND.

The SLN is identified by intraoperative lymphoscintigraphy with the use of a handheld gamma counter and by direct visualization of blue-stained tissue (Figure 1) in the draining lymphatic basin after intradermal injection of a radioactive tracer (technetium Tc 99m [99mTc] sulfur colloid) and isosulfan blue around the primary melanoma biopsy site. The use of the blue dye in combination with the radioactive colloid has been demonstrated to lead to optimal detection and identification of the SLNs.

Since only 15% to 20% of patients with a positive SLN biopsy specimen are found to have further metastatic disease in the CLND specimen, many authors have sought to identify prognostic factors that predict the residual nodal basin disease status after SLN biopsy before CLND and, thereby, limit CLND to patients with probable further metastases. Previous multi-institutional and single-institution studies have concluded that primary tumor features, such as thickness or ulceration, cannot reliably identify patient subpopulations with minimal risk of metastatic disease in the nonsentinel nodes. More recently, Reeves et al used a more complex scoring system that combines primary tumor ulceration and size of SLN metastases. They concluded that patients with a score of 0 are unlikely to have nonsentinel node metastases or to benefit from CLND. Since only 21 patients were included in this group, however, this recommendation requires validation in larger studies.

We have questioned whether the finding of histologically negative lymph nodes together with histologically positive SLNs in the biopsy specimen accurately predicts the absence of further metastasis in the remaining nodes in the sampled basin, and consequently eliminates the necessity for CLND.

Figure 1. Intraoperative photograph of a sentinel lymph node and the afferent lymphatic. Note the isosulfan blue staining of the sentinel node and the afferent lymphatic.

METHODS

PATIENTS

We reviewed the records of the Department of Pathology database and the Department of Surgery case log at the Massachusetts General Hospital, Boston, to identify all patients who underwent intraoperative lymphatic mapping for cutaneous melanoma with a primary tumor thickness of greater than 1 mm or invasive to Clark level IV or greater. This identified 506 consecutive patients treated between January 1, 1997, and May 31, 2003. None of the patients had clinical evidence of metastatic melanoma at the time of their lymphatic mapping as assessed by clinical history and physical examination findings. All of these patients underwent SLN biopsy with the plan to perform CLND if SLN metastases were identified; none of these patients underwent an initial ELND.

Of these patients, we identified and further evaluated the subgroup that had histologically positive SLNs. The pathological characteristics of the primary melanoma, the number of nodes recovered during SLN biopsy, the number of nodes with evidence of metastatic melanoma, the number of patients who underwent CLND after SLN biopsy, and the pathology reports of the CLND specimens were reviewed.

SLN MAPPING TECHNIQUE

The technique of SLN mapping was previously reported in detail by Gadd et al. In brief, approximately 3 hours before the operation, 99mTc sulfur colloid (CIS-US Inc, Bedford, Mass) was injected into the dermis surrounding the site of the primary melanoma or biopsy scar. The total dose was typically divided into 4 equal parts. Planar gamma images were obtained 5 to 60 minutes after injection to define the location of the SLNs. In the operating room, most patients then received an injection of 0.5 to 1.5 mL of 1% isosulfan blue vital dye (Lymphazurin; Zenith Parenterals, Rosemont, Ill) into the dermis circumferentially around the biopsy scar or melanoma. A handheld gamma detector (Care Wise Medical Products, Morgan Hill, Calif, or Neoprobe Corp, Dublin, Ohio) was used intraoperatively to precisely identify the location of the SLNs. Sentinel lymph nodes were defined as those that were stained with Lymphazurin dye and/or concentrated 99mTc sulfur colloid. Acceptable basin counts after SLN excision were defined as less than 10% of the counts of the most radioactive lymph node. In all patients, the entire SLN was immediately placed into isotonic sodium chloride solution. The primary melanoma site was widely reexcised during the same operation in most patients.
Details of the lymph node analysis have been previously reported. Briefly, 3 serial tissue sections, each 4 mm thick, were obtained from the paraffin-embedded lymph node tissue blocks at 3 levels 80 mm apart. One section was stained with hematoxylin-eosin. The remaining sections were subjected to immunohistochemical analyses. Further unstained sections from the third level were kept for repeat staining if necessary.

A diagnosis of metastatic melanoma was made when all of the following criteria were fulfilled: (1) individual cells in a linear array or nests of epithelioid or spindle cells foreign to the lymph node were present; (2) the cells demonstrated cellular atypia defined as cellular enlargement, prominent nuclei, nuclear pleomorphism, or dusty cytoplasmic melanin granules; (3) positive staining was present for 1 or more of the melanocytic markers S-100, HMB-45, NKIC3, or MART-1; and (4) the cells in question could be identified on the hematoxylin-eosin–stained sections.

A diagnosis of capsular nevus was made when all of the following criteria were fulfilled: (1) individual cells in a linear array and/or nests of epithelioid or spindle cells foreign to the lymph node were present; (2) the cells demonstrated no cellular atypia; (3) the cells showed positive staining for 1 or more of the melanocytic markers S-100, HMB-45, NKIC3, or MART-1; and (4) the cells in question could be identified on the hematoxylin-eosin–stained sections.

A diagnosis of metastatic melanoma was made when all of the following criteria were fulfilled: (1) individual cells in a linear array or nests of epithelioid or spindle cells foreign to the lymph node were present; (2) the cells demonstrated no cellular atypia; (3) the cells showed positive staining for 1 or more of the melanocytic markers S-100, HMB-45, NKIC3, or MART-1; and (4) the cells in question could be identified on the hematoxylin-eosin–stained sections.

HISTOLOGIC AND IMMUNOHISTOCHEMICAL ANALYSIS

Categorical data were examined in a univariate analysis by means of the chi-square test; continuous data were analyzed by unpaired t test or Mann-Whitney test.

STATISTICAL ANALYSES

Examination of the SLN biopsy specimen identified 87 patients with metastatic melanoma; these patients had SLNs in 94 regional nodal basins (a range of 1 to 3). The clinical and pathological characteristics of those patients are summarized in Table 1. The number of nodes procured from each basin during SLN biopsy ranged from 1 to 10 (mean ± SD, 3.20 ± 2.13), and the number of positive nodes identified in the SLN specimen ranged from 1 to 3 (1.19 ± 0.45). After identification of metastasis in the SLN biopsy specimen, all patients were offered CLND and interferon chemotherapy; 80 patients (92%) underwent CLND. Of the other 7 patients, 3 had 8 or more histologically negative SLNs harvested at the time of SLN biopsy and were considered to be at low risk for further lymph node metastasis; 3 refused further surgical treatment; and 1 was lost to follow-up. Only 1 of the 6 patients available for examination had evidence of recurrence that was not in the sampled nodal basin (iliac nodes), but in the axilla (after a follow-up of 6-47 months).

Twelve (15%) of the 80 patients who underwent CLND were found to have further metastases in the final surgical specimen. No significant differences in the primary tumor characteristics for these patients were identified when compared with those with negative CLND (Table 1).

We further assessed the patients with positive SLN biopsy specimens by grouping them on the basis of the number of positive SLNs and the presence of negative lymph nodes in the SLN biopsy specimen submitted. Twenty-eight SLN specimens from patients who underwent CLND included only histologically positive nodes (1, 2, or 3). Seven of these patients (25%) had additional nodes with metastatic melanoma in the CLND specimen (Table 2). The other 52 patients in whom CLND was done had negative nodes along with 1 (n=48, 92%) or 2 (n=4, 8%) positive SLNs.

The 48 patients who had CLND and who had only 1 positive SLN also had 1 to 9 histologically negative nodes in the SLN biopsy specimen per sampled basin. Four (8%) of these patients had additional nodes with metastastic

### Table 1. Patient, Tumor, and SLN Characteristics of Patients With a Positive SLN

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Negative CLND</th>
<th>Positive CLND</th>
<th>No CLND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients No.</td>
<td>68</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>37/31</td>
<td>6/6</td>
<td>6/1</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>46.29 ± 15.31</td>
<td>50.16 ± 17.54</td>
<td>46.57 ± 14.18</td>
</tr>
<tr>
<td>Primary tumor site, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>29</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>14</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>15</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Head/neck</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Primary tumor criteria*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration, No.</td>
<td>22</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Ulceration, median ± SD, mm</td>
<td>2.85 ± 3.58</td>
<td>6.40 ± 3.79</td>
<td>0.5</td>
</tr>
<tr>
<td>Thickness, median ± SD, mm</td>
<td>2.5 ± 1.70</td>
<td>3.9 ± 2.28</td>
<td>1.79 ± 0.29</td>
</tr>
<tr>
<td>Clark level, median ± SD</td>
<td>4 ± 0.42</td>
<td>4 ± 0.63</td>
<td>4 ± 0</td>
</tr>
<tr>
<td>SLN site, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axilla</td>
<td>42†</td>
<td>4</td>
<td>6†</td>
</tr>
<tr>
<td>Groin</td>
<td>16</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Head/neck</td>
<td>15†</td>
<td>1</td>
<td>3†</td>
</tr>
</tbody>
</table>

Abbreviations: CLND, completion lymph node dissection; SLN, sentinel lymph node.
*No significant difference was found when any of these characteristics were compared between the 3 groups by unpaired t test.
†Three patients had 2 basins (2 axilla and neck, and 1 both axillae), and 1 patient had 3 basins (neck and both axillae).
‡Two patients had 2 basins (one in axilla and neck, and the other in both axillae).
melanoma in the CLND specimen (Table 3). The 4 patients who had CLND with 2 positive SLNs had 2 to 4 negative SLNs. Of this group, 1 (25%) was found to have further positive nodes on CLND (Table 3). These data thus showed that patients with only positive nodes obtained during SLN biopsy had a statistically significantly greater chance (25%) of having further positive nodes on CLND than did patients with both positive and negative nodes on SLN biopsy (10%). This increased risk was most pronounced when the former group (positive nodes only) was compared with patients whose SLN biopsy had shown only 1 positive node plus negative nodes (8% metastases on CLND). Nevertheless, no patient subgroup with any SLN metastasis was found to have minimal risk of further metastases in the CLND specimen.

We also questioned whether the proportion of positive vs total nodes in the SLN specimen might accurately predict the status of the remaining nonsentinel nodes. The number of negative nodes obtained from the same basin as the positive node(s) in SLN biopsy specimens ranged between 1 and 9. The proportion of positive vs total ranged from 1 of 2 to 1 of 10 in the negative CLND subgroup, and from 1 of 2 to 1 of 4 in the positive CLND subgroup (Figure 2). This analysis, therefore, did show that no patients with a positive to total SLN proportion of greater than 1 of 4 had further metastases found on CLND. However, since only 9 patients fit this criterion in our study, the clinical validity of this observation will require further evaluation.

**COMMENT**

Sentinel lymph node mapping and biopsy has been enthusiastically adopted as the most precise method for staging primary cutaneous melanoma of 1.0 mm thick or greater, or Clark level IV or greater. It is a minimally invasive and highly accurate procedure for identifying occult nodal metastasis and thus significantly influences the prognosis and survival of these patients. Approximately 80% of patients are determined to be node negative by this technique and can be predicted to have a 5-year disease-free survival rate of 65% to 95% (depending on other primary tumor characteristics) without further therapy.3 Completion lymph node dissection is currently recommended for the remaining 15% to 20% of patients with demonstrated SLN metastases, on the assumption that clearing the regional node basin of microscopic disease will improve their survival. Admittedly, studies have shown this survival benefit only when this subgroup of patients is compared with patients undergoing delayed lymph node dissection at the time of clinically evident lymph node metastasis.4 Thus, the validity of this assumption is dependent on prospective randomized trials that are under way.25

Although some authors have suggested that routine CLND should not be recommended until results of these trials are available, most clinicians and patients find it unacceptable to proceed with simple observation after the finding of a positive SLN biopsy specimen. Various literature reports have noted that 8% to 50% of patients with positive SLNs will be found to have further metastases in the final surgical specimen.20,26 In our experience, 12 (15%) of 80 patients with a positive SLN biopsy specimen were found to have further metastasis on CLND. It should be emphasized that CLND specimens are analyzed only by the lymph node “bivalve” technique, and thus some positive nodes were probably missed. Therefore, the incidence of further metastases in the CLND specimen may even be higher. Since no diagnostic criteria are currently available to identify this subgroup and spare the remaining SLN-positive patients the costs and morbidity of CLND, CLND remains the uniform recommendation for all patients with positive SLNs.
Our review identified 3 criteria in patients with histologically positive SLN that significantly lower their risk for further metastasis on CLND: first, and most appreciably, having negative nodes together with positive SLNs in the initial SLN biopsy specimen; second, having only 1 positive SLN; and third, having a proportion of positive to total SLNs of greater than 1 to 4. Nevertheless, further lymph node metastases on CLND were present in 10% of even patients with the most significantly correlated criteria (negative nodes in the SLN specimen). This was a significantly lower risk than that in the group of patients with only positive SLNs, 25% of whom had further metastases in the CLND specimen.

This review has confirmed that this subgroup of patients (with histologically positive SLNs and negative non-sentinel nodes in the initial SLN biopsy specimen) is at significantly lower risk for further metastasis, but CLND cannot be safely omitted even for these patients.

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This study was presented at the 84th Annual Meeting of the New England Surgical Society; September 19, 2003, Newport, RI, and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

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REFERENCES


DISCUSSION

Blake Cady, MD, Providence, RI: I think this brings up the whole issue of what is a positive lymph node. Is it immunohistochemistry only? Is it some size by histochemistry? Is it a certain number of cells? Is it hematoxylin-eosin? As you know, American Joint Committee on Cancer, sixth edition, in breast cancer says that cells that are metastatic less than 0.2 mm in diameter characterizes N0 because there are no data that indicate that those patients have an adverse prognosis and I suspect somewhat similar to what may be found in melanoma. The question I have is, are your data based on the size of the sentinel node metastases? That applies both to the sentinel node that is positive and to the nonsentinel node that is positive. In other words, you might be calling some of these patients with a positive nonsentinel node positive on the basis of a few cells in the capsule.

In breast cancer there is a very important trial going on that is having difficulty recruiting, the Z-11 trial by the College of Surgeons. In that trial a positive sentinel node is randomized to axillary dissection vs observation. I believe there is also a trial in melanoma. It is the College of Surgeons, and are there any preliminary data from that? I wonder what your thoughts are about that.

Dr Elias: Others have attempted to evaluate the nodes based on the size of metastases. There is a recent publication by Reeves et al (Reeves ME, Delgado R, Busam KJ, Brady MS, Coit DG. Prediction of non-sentinel lymph node status in melanoma. Ann Surg Oncol. 2003;10:27-31), where they designed a scoring system based on the size and the ulceration of the lesion. Patients with positive nodes had significantly higher scores. Again, I am referring to the size of the metastases in the SLN, which is similar to what you have mentioned about breast cancer (new American Joint Committee on Cancer guidelines), although that study did not have a large number of patients, and again I guess the jury is still out on that issue.
Robert Osteen, MD, Boston, Mass: I have a similar question to Blake’s. Did you process the nonsentinel nodes the same way you processed the sentinel nodes? Our pathologists process the sentinel nodes by step section, the hematoxylin-eosin, and the negative nodes then get immunohistochemistry. They would not process the nonsentinel node with immunohistochemistry, so you may be prejudicing yourself by not processing the nonsentinel nodes the same way.

Dr Elias: That is true. Most of CLND nodes are not processed the same way, although the nodes that I have referred to in my presentation as the negative nodes in the SLN specimen were nodes processed the same way as the SLN in our study. When we compare the groups with positive only vs positive and negative nodes, these are all nodes processed with both hematoxylin-eosin and immunohistochemistry.

Harold Wanebo, MD, Providence: In the group that had the combined sentinel node negative and positive, the negative sentinel nodes were part of the same process. They were identified either by the blue dye or you used the gamma probe detector, one of those, so they were presumably positive nodes but only one was positive. Is that right?

Dr Elias: Correct.

Dr Wanebo: So they all had characteristics for being in the sentinel node area. The question is, do you have a feeling that maybe the number that is looked at, for example, if one did 4 or 5 nodes in that area and the rest of those were negative, is relevant to whether a subsequent dissection would be needed? This might provide a rationale to avoid a subsequent procedure of which 90% are probably unnecessary.

Dr Elias: As I have mentioned, we evaluated the ratio of positive to total number of nodes. When we had a higher number of nodes, the ratio will be lower. This was noted only in the negative completion group. A ratio of 1 to 4 or greater had only negative CLND; thus, it might be beneficial to get more than 1 or 2 nodes. But looking at our data: the earlier specimens from 1997 had higher numbers of nodes than the more recent specimens. As we have more experience with this, more surgeons feel more comfortable taking only 1 or 2 nodes, and when these are negative, no further nodes are needed.

Thomas Colacchio, MD, Lebanon, NH: Did you look at the group that didn’t have CLND and evaluate for any clinical recurrences, and did you apply your criteria to that group to see if you could have predicted whether the recurrences would have occurred?

Dr Elias: Actually, we did. Only 1 out of the 7 patients, with up to 47 months of follow-up, had recurrence. We lost 1 patient to follow-up, so we do not have any further data on him, but the other 5 do not have any recurrences.

ARCHIVES OF INTERNAL MEDICINE

Evaluation of the Benefits and Risks of Low-Dose Aspirin in the Secondary Prevention of Cardiovascular and Cerebrovascular Events

Steven M. Weisman, PhD; David Y. Graham, MD

Background: In spite of the clear evidence of benefit of aspirin in the secondary prevention of cerebrovascular and cardiovascular thrombotic events, its use in patients at high risk due to a previous event remains suboptimal. A possible explanation for this underuse is concern regarding the relative benefit in relation to the potential risk for serious gastrointestinal events.

Objective: To compare the benefit and gastrointestinal risk of aspirin use for the secondary prevention of thromboembolic events.

Design: A meta-analysis was conducted using 6 trials (6300 patients) meeting the inclusion requirement of use of low-dose aspirin (≤325 mg/d) in approved secondary prevention indications.

Results: Aspirin reduced all-cause mortality by 18%. In addition, aspirin use reduced the number of strokes by 20%, myocardial infarctions by 30%, and other “vascular events” by 30%. Alternately, patients who took aspirin were 2.5 times more likely than those in the placebo group to have gastrointestinal tract bleeding. The number needed to treat for aspirin to prevent 1 death from any cause of mortality was 67, while 100 needed to be treated to detect 1 nonfatal gastrointestinal tract bleeding.

Conclusion: Aspirin use for the secondary prevention of thromboembolic events has a favorable benefit-to-risk profile and should be encouraged in those at high risk. (2002;162:2197-2202)

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