Routine Imaging of Asymptomatic Melanoma Patients With Metastasis to Sentinel Lymph Nodes Rarely Identifies Systemic Disease

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Hypothesis: The diagnostic yield of chest radiography; computed tomography (CT) of the chest, abdomen, and pelvis; and CT or magnetic resonance imaging of the brain in the initial evaluation of melanoma with metastasis to sentinel lymph nodes may not identify systemic disease.

Design: Retrospective analysis.

Setting: Tertiary care referral center.

Patients: Of 1183 patients identified from a database of individuals who underwent selective sentinel lymphadenectomy for primary melanoma (Breslow thickness, 0.2-30 mm), we studied 185 with at least 1 sentinel lymph node positive for metastatic melanoma (Breslow thickness, 0.8-14.5 mm).

Interventions: Chest radiography; CT of the chest, abdomen, and pelvis; and CT or magnetic resonance imaging of the brain after selective sentinel lymphadenectomy with positive sentinel lymph nodes. The medical records of the 185 patients were systematically reviewed by 4 physician reviewers, and data were extracted primarily from pathology and radiology reports.

When medical records were unavailable, information was taken from formal clinic and inpatient progress notes.

Main Outcome Measure: Diagnostic yield of imaging studies.

Results: The results of 0.5% of the imaging studies were positive for metastatic disease, 86% were negative, and 14% were indeterminate. Indeterminate results were confirmed to be negative by additional studies ranging from repeated imaging to invasive procedures, including thoracotomy and brain biopsy. The yields are as follows: chest radiography, 0%; chest CT, 0.7%; abdominal and pelvic CT, 0.7%; brain CT, 0%; and brain magnetic resonance imaging, 0%. Only 1 patient (0.5%) had detectable metastatic disease, and he had symptoms of systemic disease at the time of imaging.

Conclusions: Computed tomography of the chest, abdomen, and pelvis, and brain rarely reveals systemic metastasis at the time of selective sentinel lymphadenectomy. Routine imaging of asymptomatic patients at the time of selective sentinel lymphadenectomy is not indicated.

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SELECTIVE SENTINEL LYMPHADENECTOMY (SSL), as introduced by Morton et al., has become the standard procedure for staging the regional draining lymph nodal basins in malignant melanoma, and it has been applied to other solid tumors, including breast cancer and Merkel cell carcinoma. Although it has been established as the definitive staging procedure in melanoma, many questions about SSL remain unanswered. Particularly interesting is the subgroup of patients without palpable lymphadenopathy but with evidence of regional metastasis to the sentinel lymph nodes (SLNs).

Patients with melanoma metastatic to SLNs typically undergo completion (radical) lymph node dissection (CLND) of the corresponding lymph node basin for regional control of disease and possibly for an increase in survival. Several retrospective studies have shown that there may be a small survival advantage in patients who undergo CLND when there is no clinically palpable lymphadenopathy. However, there is much controversy in this area, as 3 other prospective studies have not shown this benefit.

Furthermore, the management of systemically metastatic melanoma (American Joint Committee on Cancer M1 disease) is essentially nonsurgical. Chemotherapy or interleukin 2–based therapies are the mainstays of systemic treatment for nonresectable melanoma, carrying a poor prognosis with or without systemic treatment.

Selective sentinel lymphadenectomy allows for evaluation of the status of
regional lymph nodes in conjunction with resection of the primary lesion, reserving dissection of the entire nodal basin for patients with positive SLNs. Unlike in many other cancers, this allows for local staging before the more invasive and morbid CLND. Local staging aside, knowledge of the presence of distant disease is important and may obviate the need for local control or indicate a more aggressive neoadjuvant therapy. With respect to the evaluation of distant disease, the question becomes when and how to search for it. Typically, many clinicians stage patients immediately on diagnosis. Depending on the cancer, this philosophy may or may not have clinical utility. In patients with colon or gastric cancer, the argument can be made that 10% to 20% of patients will have metastatic disease at initial presentation and, therefore, that staging is appropriate on initial diagnosis because it will determine how far the therapy for local control should be taken. In most cases, metastatic disease is a contraindication to surgery other than for palliation. With melanoma, CLND might not be performed if there is previous knowledge of distant metastatic disease. In this case, most physicians would proceed to systemic therapy.

Numerous studies and recommendations have been published on the appropriate radiographic studies for detecting stage IV disease in patients with melanoma. Most of these articles come from the “pre-SLN era” and have questionable applicability in patients who have been staged by examination of their SLNs (Table 1). Most studies do not stratify by stage or group several other malignancies into the analysis; none effectively examine the subgroup of patients with newly diagnosed melanoma metastatic to SLNs. However, although much of the data are conflicting, they provide some insight into the current radiographic staging practices in place across the United States.

### CHEST RADIOGRAPHY

Chest radiography as a staging procedure for melanoma has been evaluated in 2 recent studies. Hofmann et al examined 524 patients with melanoma without physical evidence of stage IV disease at the time of diagnosis and found only 1 true positive (0.2%) and 23 false positives (4.4%). Buzaid et al, in their 1995 study primarily showed that in 96 asymptomatic patients with clinical evidence of local-regional disease (eg, palpable lymph node involvement), 2 chest radiographs (2.1%) revealed evidence of metastasis, without any false positives.

### COMPUTED TOMOGRAPHY

In 1984, Silverman et al examined 70 patients with Clark level III, IV, or V melanoma using computed tomography (CT) of the abdomen and pelvis. These patients were selected primarily based on symptoms and were studied at varying times after the primary melanoma diagnosis. Enlarged lymph nodes were detected on CT in 24%, 33%, and 75% of patients with Clark levels III, IV, and V, respectively. In addition, hepatic and splenic metastases were detected in 25% of patients with Clark level V. An unspecified fraction of these patients had radiographic findings confirmed by tissue biopsy. There was no analysis or report of false positives. Based on this study, CT was recommended for the staging of thick melanomas, but timing was not considered.

The 1995 study by Buzaid et al also analyzed the role of CT in 89 symptomatic patients who had melanoma with clinical evidence of local-regional metastasis but normal findings on chest radiography and a normal lactate dehydrogenase concentration. Computed tomography of the chest, abdomen, and pelvis yielded 6.7% true positives and 22.0% false positives. Chest CT alone detected metastatic disease in 1 patient (1.1%) with normal findings on chest radiography. Abdominal and pelvic CT revealed 5 true positives (5.6%). These patients included those who presented with regional lymph node metastasis and those with longer periods of follow-up whose first recurrence was in a regional lymph node basin. Because symptomatic patients were included in the study by Silverman et al and patients with locoregional disease in the study by Buzaid et al, the applicability of these study results to initial staging is questionable in the SLN era.

### BRAIN IMAGING

Computed tomography and, more recently, magnetic resonance (MR) imaging have been used to evaluate the brain

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**Table 1. Studies Evaluating Chest Radiography, CT, and MR Imaging for the Staging of Melanoma**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Source</th>
<th>Patients, No.</th>
<th>Staging</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiography</td>
<td>Hofmann et al,13 2002</td>
<td>524</td>
<td>Primarily stage I and II</td>
<td>0.19% Yield</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.4% False positive</td>
</tr>
<tr>
<td></td>
<td>Buzaid et al,12 1995</td>
<td>96</td>
<td>Presence of N1-N3 disease</td>
<td>2.1% Yield</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0% False positive</td>
</tr>
<tr>
<td>Chest CT</td>
<td>Buzaid et al,12 1995</td>
<td>89</td>
<td>Presence of N1-N3 disease</td>
<td>1.1% Yield</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal chest radiographic findings and LDH levels</td>
<td></td>
</tr>
<tr>
<td>Abdominal pelvic CT</td>
<td>Silverman et al,11 1984</td>
<td>70</td>
<td>Clark level III-V</td>
<td>24%-75% LAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25% of Clark level V with liver/spleen metastasis</td>
</tr>
<tr>
<td>Brain MR imaging/CT</td>
<td>Schouten et al,14 2002</td>
<td>150</td>
<td>Presence of N1-N3 disease</td>
<td>6.7% Yield</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal chest radiographic findings and LDH levels</td>
<td>22% False positive for CT C/A/P</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT, computed tomography; LAD, lymphadenopathy; LDH, lactate dehydrogenase; MR, magnetic resonance.
for metastases. The study by Buzaid et al\textsuperscript{12} also looked at CT and MR imaging of the brain and found a 1.1% yield. Schouten et al,\textsuperscript{14} in 2002, analyzed 150 patients with melanoma who underwent brain imaging as a subgroup of a larger, multidisease study without regard to stage and up to more than 5 years after diagnosis in the Netherlands. At 1 and 5 years, the estimated cumulative incidence of brain metastasis was 4.0% and 7.2%, respectively (Table 1).

As a general recommendation after reviewing the literature, Gershenwald et al,\textsuperscript{15} recommended that patients who have clinical evidence of regional disease undergo chest radiography, CT of the abdomen, MR imaging of the brain, CT of the pelvis for lower extremity melanomas, and CT of the neck for head and neck melanoma. The low yield and high false-positive rate of CT is acknowledged, but it is recommended to provide a baseline for future studies, that is, so that false-positive scans will be culled out by virtue of being unchanged at follow-up. At MD Anderson, diagnostic imaging for patients with positive SLNs has followed in the spirit of the recommendations of Gershenwald et al\textsuperscript{15} and others, with most patients undergoing chest radiography; CT of the chest, abdomen, and pelvis; and CT or MR imaging of the brain.

An argument in favor of early imaging is that it is only a matter of cost and that there is no downside; however, this is not necessarily true. If imaging results are abnormal, the physician is obligated to perform another test or a biopsy until a definitive result is obtained. Depending on the false-positive rate, many unnecessary tests are potentially performed to arrive at a definitive stage. Consideration of this risk-benefit ratio is central to deciding whether radiographic staging is worthwhile after the detection of positive SLNs. To evaluate the overall yield of these studies, we retrospectively reviewed our experience with radiographic imaging in patients with positive SLNs following SSL.

**STUDY DESIGN**

A retrospective analysis of all patients with melanoma who underwent SSL at a single tertiary care referral center during a 9-year period (April 6, 1994, to February 18, 2003) was performed, with follow-up ranging from 5 months to 10 years. At the time of SSL, all patients underwent chest radiography. From this group, individual patients who had pathologic evidence of metastasis to at least 1 SLN were identified. Medical records were reviewed, and patient demographics, characteristics of their primary tumor, and findings from radiographic studies were analyzed.

**RADIOPHGRAPHIC TESTS**

Of the patients in whom a positive SLN was identified, outcomes of the following imaging studies were recorded: chest radiograph; CT of the brain, chest, abdomen, and pelvis; and MR imaging of the brain. To ensure that the imaging studies were relevant for analysis around the time of SSL, inclusion criteria required that the studies occurred after tissue diagnosis and at the latest 3 months after SSL negative test results, and indeterminate test results that ultimately proved to be negative were permitted if the tests were performed after 3 months, as it was assumed that patients would not have had metastatic disease at the time of diagnosis; these data points were in the minority. Data on repeated imaging and operative procedures used to evaluate findings on the imaging studies were also recorded.

**DATA ANALYSIS**

Imaging results were categorized as positive, negative, or indeterminate. Positive imaging results demonstrated the presence of systemic metastasis; to be considered positive without a definitive tissue sample, the images had to be clearly consistent with metastasis. Negative imaging results revealed no evidence of systemic metastasis. Indeterminate imaging studies had findings that could neither include nor exclude systemic metastasis. Diagnostic yield was calculated as the number of positive images divided by the total. In cases of indeterminate results, the type and result of confirmatory testing was used to determine whether the initial study result was truly positive or negative. Confirmation consisted of either unchanged imaging studies at follow-up or negative biopsy results.

**RESULTS**

**PATIENT CHARACTERISTICS**

From a database, 1183 patients were identified as having undergone SSL for melanoma between April 6, 1994, and February 18, 2003. These patients were 62% men, with a mean (SD) age of 54.8 (16.3) years. A total of 185 patients (16%) had pathologic evidence of metastasis to at least 1 SLN and were included in the study; 67% of these patients were men, with a mean (SD) age of 50.1 (16.8) years, and 26% were confirmed to be dead.

Data on the 185 patients’ primary tumors (Clark level, Breslow thickness [T stage], and location) and the numbers of positive SLNs are presented in the Figure. None of the patients had positive findings on initial chest radiography.

**IMAGING STUDIES AND ADDITIONAL PROCEDURES**

A total of 142 patients (77%) underwent chest CT. Findings from 1 examination (0.7%) were positive, from 114 (80%) were negative, and from 27 (19%) were indeterminate. Twenty-two additional radiologic studies and 3 operations were performed to confirm that the indeterminate findings were in fact falsely positive.

Of the 185 patients studied, 146 (78%) underwent CT of the abdomen and pelvis. Findings from 1 examination (0.7%) were positive, from 123 (84%) were negative, and from 22 (15%) were indeterminate. Nineteen patients underwent additional radiologic studies, and 1 underwent an operation to confirm that the indeterminate findings were false positive.

Only 112 patients (61%) underwent evaluation of the brain at the time of SSL: 86% underwent MR imaging and 14.3% underwent CT. None of the findings were positive, 105 (94%) were negative, and 7 (6.3%) were indeterminate (Table 2). Five additional radiographic studies and 2 operations were performed to confirm all indeterminates as false positive.

Only 1 patient (0.5%) had radiographic evidence of systemic metastasis on imaging at the time of SSL (Table 3). It is important to review the case history of...
the patient who had positive findings on initial imaging studies. This patient was a man who noticed a pigmented, nickel-sized lesion growing on his left calf. He waited 2 years before seeking medical attention; ultimately, at age 53 years, an ulcerated, 4.5-mm-thick melanoma without palpable regional lymph nodes was diagnosed. One month later he had normal findings on chest radiography and underwent left femoral SSL, revealing 2 of 5 SLNs to be positive for macrometastatic disease. His staging imaging was performed at his health maintenance organization and consisted of whole-body positron emission tomography and brain MR imaging only; the findings from both studies were negative. He then underwent CLND, yielding another 4 nodes, which were all negative. Two months after SSL he developed dyspnea, and chest radiography revealed evidence of metastatic disease. A CT of the chest, abdomen, and pelvis at that time showed numerous small metastases throughout. He subsequently underwent biochemotherapy without a substantial response and died 8 months after SSL.

To confirm indeterminate results as being either positive (true positive) or negative (false positive), 2 major treatment pathways were followed. The presence or absence of distant disease was confirmed by tissue biopsy or by assessing for growth of the lesions by repeated imaging. Completion (radical) lymph node dissection was not delayed for the results of the repeated imaging. The spectrum and number of operative procedures for indeterminate results are given in Table 4.

Patients with positive SLNs represent a special population of melanoma cases. These patients have a substantially poorer prognosis directly from an increased risk of distant spread of their tumor. This has prompted an extensive search for M1 disease in an effort to perform accurate staging. Determining which (if any) routine imaging tests are useful in treating these patients is clinically important information because it may profoundly alter how staging is performed at the time that positive SLNs are diagnosed. Furthermore, it is also interesting from a

Table 3. Characteristics of the Patient With the Positive Metastatic Evaluation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient Sample, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53</td>
</tr>
<tr>
<td>Primary site</td>
<td>Lower extremity</td>
</tr>
<tr>
<td>Breslow thickness, mm</td>
<td>4.5</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Present</td>
</tr>
<tr>
<td>SLNs, No.</td>
<td>5</td>
</tr>
<tr>
<td>Positive SLNs, No.</td>
<td>2</td>
</tr>
<tr>
<td>Nodes from CLND, No.</td>
<td>4</td>
</tr>
<tr>
<td>Nodes from CLND positive, No.</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CLND, completion lymph node dissection; NA, not available; SLN, sentinel lymph node.

Table 4. Operative Procedures for Indeterminate Results

<table>
<thead>
<tr>
<th>Operative Procedure</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open brain biopsy</td>
<td>2</td>
</tr>
<tr>
<td>CT-guided lung biopsy</td>
<td>1</td>
</tr>
<tr>
<td>Thoracotomy and wedge lung resection</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>1</td>
</tr>
<tr>
<td>Laparotomy and deep pelvic lymph node biopsy</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: CT, computed tomography.

Table 2. Results of Brain MR Imaging and CT*

<table>
<thead>
<tr>
<th>Result</th>
<th>MR Imaging (n = 96)</th>
<th>CT (n = 16)</th>
<th>Total (N = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>91 (94.8)</td>
<td>14 (87.5)</td>
<td>105 (93.7)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>5 (5.2)</td>
<td>2 (12.5)</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Extra imaging</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Operations</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; MR, magnetic resonance.

*Data are given as number (percentage).
biological perspective to elucidate the concurrent incidence of distant metastasis at the time of diagnosis of a positive SLN, which usually represents clinically occult disease.

This study examines these questions by retrospectively reviewing a large multisurgeon experience at a single tertiary care referral center. The patients in this study are demographically similar to the general melanoma patient population in North America. The extent of disease is varied but is not unlike that observed elsewhere and is, therefore, a useful study for individuals with newly diagnosed melanoma.

Five major imaging modalities were evaluated. These imaging methods are similar to those described elsewhere for melanoma staging. Because this was a retrospective review and there was not an established imaging protocol, not all patients underwent all studies. Much of this was because many patients were evaluated at other hospitals and were referred to the tertiary care center for initial management and intermittent follow-up consultations. Only a few patients underwent brain CT; most likely because as MR imaging became more available during the decade of the study, practice patterns shifted toward using MR imaging to evaluate the brain (data not shown).

The most striking outcome of the data centers around evaluation of the brain (Table 2). Melanoma has a known propensity to metastasize to the brain. None of the patients with positive SLNs had evidence of brain metastases. Only 7 studies (6%) were indeterminate; however, 2 patients (29%) went on to have negative findings on brain biopsy, a procedure with significant complication rates. Based on these data, it may be more prudent to perform brain biopsies around the time of SSL.

Initial imaging of the thorax by plain radiography revealed metastatic disease in no patients. One patient who underwent chest CT also had a second (repeated) chest radiograph that showed an interval development of metastatic disease. There are several elements of this history that are atypical of most of the other patients in this study. First, there was approximately 2 years between identification of the large pigmented lesion and receipt of definitive medical care. Although it is difficult to present accurate data on time from initial awareness of a lesion to diagnosis and treatment, waiting 2 years is likely to be an abnormally long time. He also had the symptom of dyspnea as the trigger of the imaging study. His other variables were not different from those of the remainder of the sample. His primary tumor was T4 (4.5 mm), but this was comparable to the sample, with an overall mean (SD) Breslow thickness of 3.4 (2.6) mm; he had 2 positive SLNs compared with a sample mean (SD) of 1.5 (1.1) positive SLNs.

In the context of negative findings on chest radiographs, chest CT initially offered no additional positive results. The value of chest radiography, however, goes beyond staging alone. It is a useful adjunctive test for preoperative risk stratification for morbidity directly related to operative procedures, and screening for metastases (although low yield) can be viewed as an additional benefit.

Evaluation of the abdomen had a similarly low yield. Abdominal and pelvic CT findings were positive in only 1 patient—the same one who also had positive chest CT findings. The diagnostic yields are sufficiently low that as in the case of the brain, CT of the abdomen and pelvis is not justified to be performed on every patient.

An important additional finding is the observation that given a history of melanoma, a high rate of indeterminate findings were reported by the radiologists. For CT of the chest and abdomen/pelvis, the indeterminate rates were 19% and 15%, respectively. Indeterminate rates for brain imaging (6.3%) are lower but are still high given the change in treatment and worsening of prognosis that a positive result brings. Most indeterminate imaging results were reevaluated by either repeated imaging or the addition of an alternative technique (such as positron emission tomography or ultrasound). However, in some cases, the diagnosis was obtained through operative intervention. The types of procedures performed included 2 brain biopsies, a thoracotomy, and a deep pelvic lymph node excisional biopsy (Table 4). Each of these procedures ultimately revealed no metastatic disease—the indeterminate test results were in fact false positives. Although no complications from these procedures were noted in our study, every invasive procedure comes with considerable risks of morbidity and mortality, and it is only a matter of increasing numbers before serious complications are observed.

Whereas findings from previous studies have been conflicting regarding the utility of imaging for the staging of malignant melanoma, this study provides concrete data applicable to the important subgroup of patients with metastasis to the SLNs. After retrospective analysis of a large sample of patients with melanoma who underwent SSL, it is evident that an extremely low yield is obtained from chest radiography, CT of the chest, CT of the abdomen and pelvis, and CT or MR imaging of the brain. The 1 patient in our study who had evidence of systemic metastases on imaging had an extended time to diagnosis and was noted to have symptoms of disseminated disease soon after SSL. Although retrospective studies are weaker than prospective studies, the evidence presented herein suggests the following: (1) there is no detectable systemic metastasis at the time of SSL in asymptomatic patients with melanoma in North America; (2) it is reasonable to proceed with CLND without obtaining staging imaging, except in symptomatic patients; and (3) overaggressive screening will lead to numerous false-positive results and the potential for iatrogenic harm. A more definitive conclusion may be drawn from a prospective trial.

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Dr Miranda was awarded the Resident’s Prize for this study from the Pacific Coast Surgical Association.

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REFERENCES


DISCUSSION

James E. Goodnight, Jr, MD, PhD, Sacramento, Calif: In strategic planning class, they teach you that you must have a good product, that there must be a customer base that wants the product, and, significantly, that the customer base must be able to use these clinical criteria? Must one be aggressive in searching for disease you cannot treat effectively?

Moreover, there is an “opportunity cost” to the many negative imaging studies performed. Simunovic et al (J Clin Oncol. 2004;22:217-219) remind us of 3 fundamental concepts of economics: scarcity (whatever resources are available, they are insufficient to support all possible activities), choices (because resources are scarce we must choose between different ways of using them), and opportunity cost (by choosing to use resources in one way, we forgo other opportunities to use the same resources). There is a cost to what we don’t do because we have done something else. Certainly, if a group of studies or treatments does not favorably impact the patient, the opportunity cost is high and these studies and treatments are not cost-effective. The dollars could be better spent. Could the authors have a type II statistical error in that their sample size is too small to detect a favorable yield on these staging studies? The answer is “yes,” but even if the positive yield on the imaging studies were increased by a factor of 6 or 7, the author’s conclusion would be largely the same.

Even though the study resonates with me, I do have questions for the authors:

1. An obvious question: do you think that if you added PET [positron emission tomography] scanning to the staging studies the yield would be higher?
2. Is there a Breslow thickness of the primary melanoma that would impel you to proceed with imaging studies?
3. Based on this information, what is your practice now for staging melanoma patients without clinically suspicious lymph nodes? And, will your patients accept a very limited staging workup?
4. What will be your long-term follow-up procedures for your patients with a positive sentinel lymph node that presumably go on to complete lymph node dissection?
5. As a matter of interest, what is the survival at 5 years (or another measure) of this group of patients with a positive sentinel lymph node?

Jan K. Horn, MD, San Francisco, Calif: I have always relied on Dr Leong for advice in handling some of our cases at San Francisco General Hospital. I would like to ask you an additional 2 questions. First of all, if you have positive sentinel lymph nodes, this could represent small micrometastases or it could represent that the lymph node is literally replaced by melanoma. Does that have an impact upon whether or not you would use these clinical criteria?

The other thing is that it would seem to me that establishing a baseline in the early stages of the follow-up would be important. If you don’t do these studies as the patient is registered into your system, what are you going to have for comparison at a later date?

Laura J. Esserman, MD, San Francisco: Certainly [this paper] points out a problem that we have with breast cancer as well as where we perform a lot of staging studies. Even though we usually do staging studies in the stage III patients, one has to question the value since there are so many unnecessary procedures that are generated. I think that would be true with PET as well. But I did want to ask a question about whether the purpose of staging was to make a decision about chemo-

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therapy. In the setting of gross metastatic disease, what is the effectiveness of chemotherapy, and is there reason to institute it before the patient is symptomatic? In breast cancer we are reluctant to start chemotherapy in patients who are asymptomatic because there are a finite number of cycles that can be given, and starting earlier does not improve survival.

The other reason for staging would be to find a solitary metastatic focus, which could be resected. But again, those patients who are eligible for surgical resection are those who have a longer disease-free interval and lack of development of widespread metastases and, therefore, a better chance of cure.

The last question is, were the 2 positive scans in the patients who had multiple positive nodes? Maybe a workup could be justified in that subset.

David Beatty, MD, Seattle, Wash: In patients who have positive sentinel nodes, what are the decisions that you are making clinically for these patients? Are you going on routinely to clinical lymph node dissection? Is there a difference in your decision making between dissection in the neck, the axilla, or the groin? Does the amount of disease in the sentinel node influence that decision making? If it’s only 1 node and it has 2 mm of disease, is that different from multiple nodes and many millimeters or a centimeter of disease?

Finally, does that quantity of disease in the sentinel nodes relate in any way to the positive, negative, or indeterminate groups in your metastatic workup? How do you chart your way through those difficult decisions in a situation where it is not just positive or negative sentinel node, but the quantity of disease in those nodes that influences your clinical decisions and the likelihood of metastatic disease?

Dr Leong: Let me proceed with my response to the questions raised by Dr Goodnight. Dr Goodnight, first, about the utility of PET scans. This is certainly a new imaging study on the horizon. It’s very sensitive, but the specificity needs to be confirmed. There are studies to suggest that perhaps we can just use PET scan, just one trip to the nuclear medicine department, foregoing all of the CT scans. If indeed the specificity holds up, I think this would be a very viable alternative. But in the preliminary review of our data, although we have not presented the PET scan results, the specificity is being questioned with about possibly 23% of the time indeterminate findings.

Second, about the Breslow thickness. In this particular patient with a positive scan, his Breslow thickness was 3 mm. We have not made a specific attempt to analyze the Breslow thickness with respect to the positivity, and of course we have only one patient with positivity so it is difficult to make any statistical correlation. But my intuition will speak for the fact that probably there is a relationship between Breslow and positive imaging studies.

Third, the issue of acceptance by patients: I think, with a database that is being analyzable and conclusive, if we tell our patients in an honest way that really these studies are not very reliable to predict or to indicate whether they have metastatic disease or not, and that probably at this time it might not be of any utility to them, most patients will probably go along with it. There is this tendency with the initial diagnosis of melanoma, with the fear and anxiety, the patient wants to know everything if possible to see if there is any metastatic disease. But if we can provide the patient with evidence that even these studies are not conclusive, the patients will accept that advice.

Fourth, about the follow-up, and this came up later, too, from other discussants, how do we do that? This is quite controversial. This particular patient was actually symptomatic. At the time of sentinel lymph node dissection, there was some complaint about having some fatigue and some weight loss, but we were not very impressed by these very vague complaints and we went ahead with the sentinel lymph node dissection and it turned out that he had 4 positive sentinel lymph nodes. With that we pursued further with the workup and it was found that he had positive imaging studies.

Fifth, in terms of survival, for our series with 5 years of follow-up, of about 500 patients, the patients with positive sentinel lymph nodes have a median disease-free survival of about 20 months vs patients with negative sentinel lymph nodes having a disease-free survival of 60 months, a very significant difference.

The issue of micro vs macrometastasis is very important, and we are now in the process of defining what is micrometastasis vs macrometastasis, whether less than 2 mm in the lymph node vs more than 2 mm, and if that is the case, is there a correlation between imaging studies and disease-free survival?

The baseline is a good argument to do all of these studies, but I think based on this particular presentation, we have another alternative option. That is to say, if there are indeterminate findings, we can take one step back without launching into multiple invasive procedures to find out exactly what that spot on the CT is. Three months later, repeat the scans. I think in general oncologists we are not that worried if we can wait for 3 months. If there is a slight increase, still appropriate treatment can be rendered. But if the disease is stable, then the likelihood that this is not melanoma is very high and that will put everybody at ease.

Dr Esserman asked about the effectiveness of chemotherapy. Particularly in melanoma, it is quite dismal. Chemotherapy in the traditional protocol, including DTIC [dacarbazine] and so forth, even in combination chemotherapy, is only 1%. With the introduction of interferon and interleukin 2, it increases to 10%. But the long-term survival still remains to be determined. So the impact of finding metastatic disease and being effectively treated by chemotherapy is really quite minimal. So I think from that point of view it’s not relevant. Our patient with positive scans had both chest CT and abdominal CT showing metastatic disease.

The current clinical algorithm for patients with positive sentinel lymph nodes in major melanoma centers is to proceed with a workup like what we have done and then if it is negative we would then recommend a completion lymph node dissection. The utility of completion lymph node dissection is debatable, but on retrospective analysis it appears that patients with less tumor burden in the lymph nodes tend to do better, with about 20% to 30% benefit if removed prior to the development of clinically palpable lymph nodes.

The most interesting study coming up is called a Multi-center Lymphadenectomy Trial II, being proposed by Dr Donald Morton and funded by the National Cancer Institute. This particular study will randomize patients with positive sentinel lymph nodes to 2 arms, 1 with lymph node dissection and 1 with no lymph node dissection. And for the group with no lymph node dissection, they will be followed carefully with a newly developed ultrasound technique to make sure that indeed abnormal lymph nodes can be detected earlier than just clinical palpation.

In terms of the sentinel lymph node positivity and indeterminate group of patients, we have not yet established a correlation.