Multidisciplinary Management in Primary and Metastatic Melanoma

CME Learning Objectives

After reviewing the material, the participant should be able to:

- Review the presentation, staging and pathology of melanoma
- Define current treatment tactics for metastatic melanoma
- Identify and discuss the potential value of interdisciplinary approaches to melanoma treatment
- Evaluate the potential positive impact interdisciplinary approaches to melanoma treatment may have on patient outcomes
Introduction

The prognosis of melanoma, the most common serious form of skin cancer, varies widely—from almost completely curable when detected early, to highly lethal in its more advanced stages. Stage of disease at the time melanoma is diagnosed is a major determinant of prognosis and survival. For localized melanoma (approximately 80% of all melanomas diagnosed), the 5-year survival rate is over 90%. In contrast, 5-year survival rates for regional and distant-stage disease are 65% and 15%, respectively. Although the melanoma patient’s clinical stage at diagnosis largely dictates selection of therapy, considerable variation exists in the treatment approach of individual clinicians. Melanoma is a major focus of dermatology training and practice, and dermatologists play a central role in managing melanoma through primary prevention, diagnosis, and the treatment of thinner tumors. However, the advent of multimodal therapeutic strategies, sentinel lymph node (SLN) biopsy, and the use of adjuvant therapy has made melanoma management more complex, emphasizing the need for a multidisciplinary approach to the disease.

In this monograph, three different multidisciplinary panels of expert clinicians, from geographically diverse areas of the US, discuss their individual approaches to the overall management of melanoma. A fourth panel of physicians, from the H. Lee Moffitt Cancer Center, in Tampa, Florida, moderated the discussion of cases drawn from their actual clinical practice.

To facilitate comparison of institutional approaches to treatment, the names of panel members from the Thomas Jefferson University Hospital—Kimmel Cancer Center appear as [TJU], members from the Memorial Sloan-Kettering Cancer Center appear as [MSK] and those from the University of California, San Diego—Moores Cancer Center appear as [UCSD] in the case discussion sections. The moderators from H. Lee Moffitt Cancer Center appear in italics throughout the discussion.

Based on three case studies of melanoma patients, whose disease differs by patient and clinical characteristics, a “real world” view of how melanoma is currently treated in the US emerges. Differing opinions on melanoma management are offered and their validity critiqued.

In the course of the discussion, team members—including medical oncologists, surgeons, radiation oncologists, dermatologists, and oncology nurses—provide a unique multidisciplinary perspective on state of the art practice in melanoma staging, therapy, and prognosis, which has changed for the better over the past two decades and continues to progress.

Introduction to the Updated Version

This case-based educational monograph on the multidisciplinary management of melanoma was first published in October 2008, and remains highly relevant and instructive. There have, however, been some noteworthy changes over the past two years that all clinicians involved in the management of melanoma patients should be aware of, such as the 2010 revision of the American Joint Commission on Cancer (AJCC) Staging System for melanoma. Therefore, we have updated this monograph accordingly, preserving the case-based format and the original responses of our three multidisciplinary panels of expert clinicians but adding new text to highlight how recent changes might impact the staging and management of the same cases in 2010. We hope you will find this updated version every bit as interesting and instructional as the original.
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  Medical Oncologist

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**Target Audience**
Practicing physicians with a specialty/subspecialty in: hematology/oncology, medical oncology, surgical oncology, radiation oncology, dermatology.

**Unlabeled and Investigational Usage**
The audience is advised that this continuing medical education activity may contain references to unlabeled uses of FDA-approved products or to products not approved by the FDA for use in the United States. The faculty members have been made aware of their obligation to disclose such usage.
Case Presentation 1: Management of Thin Melanoma/Changes to the 2010 AJCC Melanoma Staging System

A 45-year-old fisherman sought treatment for a changing pigmented lesion on his right calf, which he had first noticed 6 months earlier. He had no history of melanoma or other skin cancer, and his relevant medical, surgical, and family histories were all negative. A shave biopsy of the mole on his calf revealed an exophytic tumor with overlying epidermal hyperplasia (Figure 1-1). Figure 1-2, a high-power view of the tumor, shows nested and single melanocytes growing within the epidermis and extending in a sheet-like growth pattern into the underlying dermis. The cells are filling the papillary dermis, making this a Clark level III tumor. The tumor’s depth, measuring from the granular layer, is 0.8 mm. Figure 1-3 shows the presence of two mitoses (arrows), indicating the vertical growth phase of the melanoma. Tumor infiltrating lymphocytes are present but non-brisk, and the edges of the biopsy are free of tumor. The key pathologic findings are listed in Table 1-1, in the fashion employed for a synoptic pathology report. In the Table, the pathologic findings highlighted in bold are those that are key to designating the tumor as stage IA in the prior AJCC staging system or stage IB in the new 2010 system. Other pathologic findings are listed in Table 1-1, the pathology findings highlighted in bold designating a stage IA clinically node-negative melanoma. Tumor infiltrating lymphocytes are present but non-brisk, and the margins of the biopsy are free of tumor.

Table 1-1

<table>
<thead>
<tr>
<th>Key Pathological Findings- Case 1</th>
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<tbody>
<tr>
<td>Invasive Primary Cutaneous Melanoma</td>
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<tr>
<td>• Tumor subtype: Superficial spreading</td>
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<td>• Clark level: III</td>
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<tr>
<td>• Breslow thickness: 0.8 mm</td>
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<tr>
<td>• Ulceration: Absent</td>
</tr>
<tr>
<td>• Mitotic rate: 2 per sq mm</td>
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<tr>
<td>• Evidence of regression: Absent</td>
</tr>
<tr>
<td>• Vertical growth phase: Present</td>
</tr>
<tr>
<td>• Angiolymphatic invasion: None noted</td>
</tr>
<tr>
<td>• Tumor infiltrating lymphocytes (TIL): Present, non-brisk</td>
</tr>
<tr>
<td>• Margins: Peripheral and deep edges of biopsy free of tumor</td>
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</tbody>
</table>

Pathologic staging: T1a NX MX (prior AJCC system)  
T1b NX MX (2010 AJCC system)
**What margin of excision would you recommend for this patient with thin melanoma?**

**Dr Berger [TJU]:** I would recommend a 1-cm margin of excision for this < 1 mm-thick melanoma.

**Dr Mastrangelo [TJU]:** I would adhere to the standard of care for a lesion of this type—ie, excision with a 1-cm margin around the primary site.

**Dr Coit [MSK]:** I would recommend a 1-cm surgical margin for this patient, if it could be achieved with primary closure.

**Dr O’Grady [UCSD]:** I would recommend a 1-cm marginal excision.

**Dr Easter [UCSD]:** I also agree. I think that a 1-cm margin would be adequate.

**Dr Sondak:** The treatment of the primary melanoma was as suggested. Wide excision with a 1-cm margin was performed.

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**Surgical Margins for Thin Melanomas**

In the early years of the 20th century, all melanomas were treated by very wide excision, taking margins of normal skin for 5 cm beyond the visible edge of the tumor or biopsy site. In the 1970s and 1980s, a series of prospective randomized trials questioned that practice, and the results of those trials made it clear that lesser margins were associated with equally good outcomes. Today, the Breslow’s thickness, a histopathologic measurement of tumor depth beginning from the granular layer of the epidermis to the deepest contiguous melanoma cell, is the primary factor taken into consideration in recommending the width of the excision margin for primary melanomas. Now it is rare to take more than 2 cm margins around the visible edge of a melanoma or its biopsy site. For example, in the World Health Organization randomized trial comparing margins of 1 versus 3 cm, patients with thin melanomas (≤ 1 mm in thickness) were found to be equally well treated with the narrower 1 cm margin than with the more radical 3 cm margin.1 This 1 cm excision margin, as done in this case presentation, has been widely adopted for thin melanomas around the world; it can almost always be closed primarily and can be done under local anesthesia in many cases if no surgical staging of the lymph nodes is indicated. For most melanomas over 1 mm in thickness, a 2 cm margin is taken. However, particularly for melanomas between 1 and 2 mm in thickness, many surgeons will consider a margin of 1 or 1.5 cm if doing so will lead to a superior functional outcome or avoidance of the need to place a skin graft. Commonly followed guidelines, such as those promulgated by the National Cancer Center Network (NCCN), reflect these principles and are firmly based on evidence from a series of randomized trials and extensive clinical experience.2

**References:**


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**Should sentinel lymph node biopsy be performed on this patient? What workup should be done?**

**Dr Mastrangelo [TJU]:** In my practice, the histopathology of every primary melanoma is reviewed. Although thickness is used for staging purposes, the volume of tumor in the reticular dermis or the papillary dermis is a more accurate indicator of risk. In addition, there are also two mitoses evident and, although no angiolymphatic invasion is present, a vascular network appears to underlie the lesion. Considering the volume of tumor, the mitoses, and the vascular network, I would recommend that this patient undergo SLN biopsy. A chest x-ray and blood and liver function testing, with particular attention to the level of lactate dehydrogenase (LDH), are also recommended. I would repeat these tests on a regular basis.

**Dr Berger [TJU]:** Although the tumor is stage T1a (ie, < 1.0 mm in thickness, no ulceration), I would still recommend SLN biopsy based on the number of mitoses and the vertical growth phase.

**Dr Sato [TJU]:** I basically agree with Dr Mastrangelo’s approach, particularly regarding SLN biopsy. There is a possibility of recurrence in patients with lesions ≥ 0.76 mm, which would justify SLN biopsy for this patient.

**Dr Sondak:** So, although you would not routinely recommend SLN biopsy for a
**Dr Sondak (continued):**

Patient with a 0.8 mm melanoma, you would take into account a number of different factors: penetration into the reticular dermis, vertical growth phase, and the presence of mitoses. Suppose our case study patient had a 0.8 mm, Clark level III lesion with no mitoses, would you still recommend SLN biopsy?

**Dr Berger [TJU]:** In my practice, I tend to be more aggressive regarding SLN biopsy once the lesion is ≥ 0.76 mm. In such cases, the risk of positive sentinel nodes increases. I would tell the patient that the chance of a sentinel node being positive is still very low, but that there is an increased risk when the melanoma is > 0.76 mm.

**Dr Coit [MSK]:** I estimate the likelihood of a positive lymph node in this patient at approximately 6% to 8%, given the mitotic rate, but sentinel node status does not seem to have the same prognostic relevance in patients with thin melanomas, such as this one, as it does for patients with intermediate or thick melanomas. Nonetheless, I think it’s not unreasonable to offer SLN biopsy to this patient after a discussion of the pros and cons.

**Dr Easter [UCSD]:** I would not recommend SLN biopsy, as long as the melanoma is < 1 mm thick. Nor would I recommend any extraordinary preoperative work-up for this patient.

**Dr O’Grady [UCSD]:** I agree with Dr Easter that the thickness of this patient’s melanoma does not warrant SLN biopsy.

**Dr McClay [UCSD]:** Histopathologic factors, such as mitotic index and the presence of tumor infiltrating lymphocytes, influence the advisability of SLN biopsy, even in cases of thin melanoma.

**Dr Sondak:** Sentinel lymph biopsy of the ipsilateral groin, using technetium-labeled sulfur colloid and isosulfan blue dye, was performed. The patient’s lymphoscintigram is shown in Figure 1-4. The wide excision specimen was grossly unremarkable. A scar consistent with the previous biopsy site was evident, with a small focus of residual melanoma in situ identified adjacent to the scar. However, the final pathology revealed that the margins were negative. Two inguinal sentinel nodes were removed, both of which were found to be hot and blue at the time of surgery.

**Dr Messina:** Figure 1-5 is a high-powered photomicrograph showing a single clump of pigmented atypical cells consistent with metastatic melanoma. The final report was metastatic melanoma in one of the two sentinel lymph nodes, with an estimated 1% involvement of the nodal area.

**Figure 1-4.** Preoperative radionuclide lymphoscintogram of patient 1. The primary site on the right calf was seen to drain to a single node in the right groin.

Source: Image provided by Vernon Sondak, MD

**Figure 1-5.** High-power view of sentinel lymph node showing a single clump of pigmented atypical cells consistent with metastatic melanoma (H&E, 400x).

Source: Photomicrograph provided by Jane Messina, MD
Sentinel Lymph Node Biopsy for Thin Melanoma

Predicting the outcome of a patient with clinically localized primary melanoma has historically been difficult. Many patients who seemed to have a good prognosis based on their Breslow thickness and clinicopathologic factors were noted to develop recurrence and die, while other patients with seemingly worse primary tumors did well. The recognition of the important prognostic significance of clinically occult (microscopic) metastases in the regional lymph nodes has helped explain some of the apparently paradoxical behavior of primary melanomas: even thin melanomas (ie, Breslow thickness ≤ 1.00 mm) can sometimes have nodal metastases and be at increased risk of distant spread, while thicker melanomas with negative regional nodes may have a better prognosis than otherwise anticipated. Knowing the status of the regional nodes holds implications for patient counseling, therapeutic decision-making, the design and interpretation of clinical trials, and quality assessment of health outcomes. For this reason, sentinel lymph node biopsy – performed using a combination of a radioactive tracer taken up by the lymphatic system, such as 99mTc-labeled sulfur colloid, and a blue lymphangiogram dye, such as isosulfan blue – has come to be widely used for the surgical staging of lymph nodes in patients with intermediate and thick but clinically node-negative melanomas. Its use in thin melanomas, however, has been more controversial.

Melanomas ≤ 1.00 mm in thickness now make up the majority of patients with cutaneous melanomas (81%), as reported to the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) cancer registry. While these patients generally have a good prognosis, 15% of current melanoma deaths result from metastases of thin lesions, according to SEER data. If all thin melanoma patients underwent SLN biopsy without any selection, the yield would be very low and the cost prohibitively high. Even if only patients with melanomas between 0.76 and 1.00 mm are routinely selected for SLN biopsy, a positive node is found in only approximately 5% of cases. Investigation of prognostic factors that would allow better selection of these patients, to avoid performing biopsies in the vast majority who have uninvolved SLNs, is continuing. Several potential high risk factors for SLN positivity in patients with thin melanoma have been identified, including tumor ulceration, a high mitotic rate, younger age, male gender, and the presence of a vertical growth phase. However, none of these predictors has been universally accepted. Previously, Clark’s level and the presence of regression have been suggested as predictors of high risk of nodal metastasis, but our work and that of others has shown this not to be the case. The prognostic impact of sentinel node biopsy for thin melanomas has also been called into question, but a recent study strongly supports the fact that a positive sentinel node is significantly associated with poorer disease-free and overall survival at 10 years for patients with melanomas ≤ 1 mm.

In 2010, the AJCC issued the 7th edition of its staging manual, which involved revision of the melanoma staging system. Most changes are relatively minor, but the most significant modifications relate to the staging of thin melanomas (1.00 mm). In this new system, the distinction between a T1a and T1b melanoma has changed. While the presence of ulceration still classifies a thin melanoma as T1b, the Clark’s level is no longer used for non-ulcerated melanomas. Instead, the absence or presence of mitoses is now used to classify thin, non-ulcerated melanomas as T1a or T1b respectively. In the present case, this tumor was classified as T1a in the former system by virtue of the absence of ulceration and the finding of Clark’s level III, but the current system relies on the finding of 2 mitoses per square mm to classify the tumor as T1b. It is important to note that this change was made based on the demonstrated impact on melanoma-specific survival of mitotic rate, which far exceeds the survival impact of Clark’s level. While, as previously noted, mitotic rate appears to correlate with the risk of sentinel node positivity, the new AJCC staging system does not specifically address whether decision-making regarding sentinel lymph node biopsy for thin melanomas should change as well.

Based on all available data, we believe that an otherwise healthy patient, particularly one younger than 70 years of age, with a thin melanoma between 0.76 and 1.00 mm should be considered for SLN biopsy, as was done in this case presentation. Furthermore, in our experience, the finding of mitoses in a thin primary tumor increases the risk a positive SLN will be found. It is not clear, however, whether all thin melanomas with one or more mitoses are at high enough risk of nodal spread to justify sentinel node biopsy and conversely whether the absence of mitoses in a thin melanoma should lead to a recommendation to forego sentinel node biopsy. Further research on this topic is clearly needed.

References:
3. Puleo CA, Messiah S. Cancer Control.
4. Gimotty PA, Botet M. Oncol. 2005;
7. Sondak VK, Taylor WF. Lessons learned i
Knowing there is a positive sentinel node, should any additional work-up now be done for this patient?

Dr Mastrangelo [TJU]: Metastatic melanoma in a lymph node is a biologically very significant finding; clearly, this tumor has the capacity to metastasize. If the cancer is present in the lymph node, it may well be present elsewhere in the body. At this point, I would perform CT scans of the chest, abdomen, and pelvis, with and without contrast, to determine if there were other metastatic sites. I would forego PET scanning and MRI of the brain.

Dr Berger [TJU]: I agree. When stage III disease is detected, other staging studies are advisable. I am more in favor of PET scanning than is Dr Mastrangelo.

Dr Sato [TJU]: Like Dr Mastrangelo, I also prefer CT scanning over PET scanning for more accurate disease staging. If the CT scan indicates other possible metastases, I would then order a PET scan to confirm that finding.

Dr Coit [MSK]: I would order no tests on this patient, other than those required to do safe surgery. The yield of cross-sectional body imaging and/or PET scans is extremely low for patients such as this one, so I would be inclined not to have these studies done in this patient with a thin melanoma and a micrometastasis. For a patient at higher risk for metastases, my choice of combination screening tests would be a whole-body PET scan and a noncontrast CT scan of the chest.

Dr Easter [UCSD]: Before considering lymph node dissection, I would initiate a metastatic workup, including chest, abdomen, and pelvic CT/PET scanning to establish baseline parameters. LDH and liver function tests would also be performed.

The Role of Preoperative Blood Tests and Imaging Studies

The risk that a patient presenting with a new diagnosis of melanoma will harbor detectable distant metastases is highly dependent on the clinical stage of the disease. Currently available blood tests, such as the lactate dehydrogenase (LDH) level, have a very low sensitivity and specificity; “false positive” tests far outweigh true positive values in clinical stage I and II melanoma. Other serum markers, such as S-100, have been under study, but none has yet been shown to be of value in early-stage melanoma patients. Therefore, we do not routinely advocate any melanoma-specific blood tests for patients prior to sentinel node biopsy or for patients with a microscopically positive sentinel node, as in this case presentation. Routine blood tests are ordered as necessary for the safe conduct of surgical procedures. This recommendation is in keeping with current practice guidelines.1,2

Positron emission tomography (PET) scanning, which uses a radioactive glucose derivative (18F-deoxyglucose [FDG]) as the imaging agent, is a sensitive test for detecting melanoma metastases above 5 to 10 mm in diameter, but is very nonspecific. Combining PET with CT scanning, so-called PET/CT fusion scans, provides better anatomic definition but does not eliminate false-positive results. FDG PET has several important limitations: subcentimeter pulmonary nodules are rarely clearly resolved, and the high background uptake of glucose in the brain markedly limits the detection of small brain metastases. For patients considered to be at high risk for harboring distant metastases, such as those with palpable regional nodal disease at presentation, and for patients for whom adjuvant therapy with high-dose interferon is going to be instituted, we generally recommend at PET-CT fusion scan plus a contrast-enhanced MRI scan of the brain. To better evaluate for small pulmonary metastases, a non-contrast CT of the chest can be added.

However, clinical stage I and II melanoma is associated with extremely low rates of radiographically evident but clinically occult distant metastases, and false positive findings on imaging studies are commonplace and usually far outnumber true positive results.3,5 We do not obtain routine imaging studies prior to performing sentinel node biopsy – a chest x-ray is obtained where necessary to facilitate a safe surgical procedure. Likewise, after a microscopically positive sentinel node biopsy, our routine practice is to proceed to completion node dissection without ordering any additional imaging studies. Once the patient has recovered from surgery, if they are going to receive adjuvant therapy with interferon or are being considered for an investigational protocol, imaging as described above is usually obtained.

Clinicians frequently speak of ordering imaging tests “as a baseline.” This implies that having an initial normal study will somehow make subsequent abnormal findings easier to detect, a largely unproven hypothesis in melanoma. Furthermore, the emotional burden false-positive and indeterminate findings place on patients should not be underestimated. Finally, modern cross-sectional imaging techniques are associated with biologically significant doses of ionizing radiation. Therefore, imaging tests should be ordered only when the results have a reasonable probability of altering the care provided to patients. Of course, as in this case presentation, experienced physicians – and anxious patients – can have different thresholds for defining “a reasonable probability.”

References:

Q Would a complete inguinal lymph node dissection be advisable for this patient, and what factors influence your decision of whether SLN-positive melanoma patients have further nodal surgery?

Dr Berger [TJU]: I think that, absent any opposing clinical data, this patient should undergo CLND. Although the volume of tumor in the node is very small, I would still recommend CLND.

Dr Mastrangelo [TJU]: It is important to involve the patient in the decision of whether to perform CLND. One must first consider the likelihood that disease will be present in those lymph nodes. Because the likelihood is approximately 1 in 5, there is an 80% probability that CLND will be done for no reason other than to gain additional information on the patient’s disease status.

Is there a therapeutic benefit to justify CLND in a patient such as this one? Disease in a lymph node increases the chance of disease elsewhere in the body. Although trial data have not demonstrated a statistically significant survival benefit for earlier intervention, I believe that it is better to rid the body of possible disease earlier rather than later. After explaining to the patient that edema of the leg is likely, I would opt to have the CLND performed. However, I would be sure to instruct the patient on ways to minimize the edema, for example, wearing a compression stocking immediately post-surgery for a minimum of 6 months after the procedure.

Dr Coit [MSK]: Because this patient has a very low likelihood of additional positive nodes, based on his having a very thin nonulcerated primary tumor with a very low tumor burden in the sentinel node, I would not perform CLND. A course of expectant observation would be more appropriate for this patient. This patient, at least in the short-term, has a very low-risk of recurrence. I would feel very comfortable not performing CLND but, instead, following this patient expectantly.

Dr Easter [UCSD]: Because metastasis was found in the patient’s lymph node, I would recommend CLND, partially to complete the staging and determine if there is additional disease, but also to pre-emptively clear his groin of what may be residual microscopic disease. I would perform a superficial lymph node dissection, not a deep groin dissection, which substantially increases morbidity.

Dr Linson [UCSD]: For this patient, the likelihood of finding disease in more nodes is low. I agree with Dr Easter regarding superficial dissection, because deeper resection leads to a high likelihood of long-term lymphedema, which can be quite troublesome for these patients.

Q Post-surgery, would you recommend adjuvant therapy for this patient, and what factors influence your decision?

Dr Wolchok [MSK]: This patient is, at least, a candidate for discussion of adjuvant therapy. I frame the discussion with such patients by informing them that high-dose IFN-α postoperatively can delay time to recurrence, if recurrence is destined to happen. The alternative to high-dose IFN-α is either expectant observation or participation on an experimental vaccine trial.

Nurse Roman [MSK]: We offer our patients participation in a vaccine trial. After determining their eligibility for entry into a trial, we discuss the current options.

Dr Linson [UCSD]: If the patient has high-risk disease characteristics, he might qualify for RT. I probably would not recommend adjuvant therapy in this patient.

Dr O’Grady [UCSD]: When you have to use immunohistochemistry to spot the metastasis, how significant is it? Many patients such as this one, with subcapsular, small-volume involvement of the node, tend to have good outcomes. It would be interesting to investigate the use of additional studies to find metastases in the nodes of such patients. Certainly, the thickness of this patient’s melanoma would not have suggested nodal involvement.

Completion node dissection after a positive sentinel node biopsy

This patient has a low risk of encountering identifiable metastases in non-sentinel nodes. Since identification of the metastases in the sentinel node biopsy in this case was based on immunohistochemistry—which is not routinely performed on completion node dissection specimens—routine histologic examination of the dissection specimen almost always reveals no involved non-sentinel nodes in cases like this. 1,2  Whether that means there is no or only a limited likelihood that the patient will eventually fail in the regional nodes, however, remains to be seen. In fact, a relatively young patient such as the one in this case presentation will be at risk of nodal basin failure for two decades or more, so only long-term follow-up...
of debate whether this degree of survival improvement has real world clinical impact. The delay in development of more effective therapy has engendered more controversy than adjuvant therapy per se. In the case of this patient, an informed decision about the risk of relapse and death after surgery must take into account the potential benefits and risks of adjuvant therapy, which is likely small. If we take the very favorable estimates of prognosis for the case of this patient, an informed decision about choosing therapy based on a careful and informed discussion is critical.

Many alternative approaches to adjuvant therapy of node-positive melanoma have been evaluated, but none aside from interferon have shown convincing evidence of a durable relapse-free benefit, let alone an overall survival improvement. We would consider the patient in this case presentation to be an ideal candidate for participation in an investigational trial of adjuvant therapy, such as a vaccine trial. Although several of the expert physicians in our panel of discussants have advocated adjuvant chemotherapy for melanoma, prospective randomized trial evidence to support this approach is entirely lacking and we do not advocate adjuvant chemotherapy outside of a clinical trial.

References:
Case Presentation 2: Intermediate-Thickness Melanoma with Positive Sentinel Node

A 46-year-old female commercial pilot presented with a 1.84-mm, non-ulcerated melanoma on the right lateral back, Clark level IV. The tumor extends into the reticular epidermis focally to the base of the biopsy (Figures 2-1 and 2-2). The patient had no personal history of melanoma or other skin cancers, and relevant medical, surgical, and family histories all were negative. Regression is absent, vertical growth phase is present, and tumor-infiltrating lymphocytes are present and non-brisk. No angiolymphatic invasion is evident. The mitotic rate is 26/mm². Key pathologic findings are summarized in Table 2-1, designating this as a T2a melanoma.

Q What margin of excision would you recommend for this patient with a melanoma of intermediate thickness and the pathologic features described?

Dr Coit [MSK]: This is a high-risk melanoma. The recommended margin for this patient would be 2 cm, assuming that it could be done without significant disfigurement, which is likely. One cm would be adequate, if primary closure were an issue. A margin slightly less than 2 cm would be acceptable, if not optimal, for this patient.

Dr Berger [TJU]: For melanoma of the lower back that I can probably close, I would usually do a 2 cm margin.

Dr Mastrangelo [TJU]: The margin of excision for this patient would be 2 cm; closure should not pose any technical difficulty or functional problems for the patient.

Dr O’Grady [UCSD]: This is a troublesome lesion, partially because it’s incompletely removed and extends to the base. The epithelium is very thin and there are what appear to be many melanoma cells high in the epidermis. I would recommend, at least, a 2 cm margin, with the caveat that the thickness is only an estimate. The melanoma has been removed only partially and could, indeed, be deeper.

Q Would you recommend sentinel node biopsy, and what factors influence this decision for patients with melanomas of intermediate thickness?

Table 2-1

Key Pathological Findings- Case 2

Invasive Primary Cutaneous Melanoma

- Tumor subtype: Superficial spreading
- Clark level: IV
- Breslow thickness: At least 1.84 mm (to deep margin)
- Ulceration: Absent
  - Evidence of regression: Absent
  - Vertical growth phase: Present
  - Angiolymphatic invasion: None noted
- Mitotic rate: 26 per sq mm
- Tumor infiltrating lymphocytes (TIL): Present, non-brisk

Pathologic staging: T2a NX MX
Dr Coit (MSK): SLN biopsy can be recommended for this patient with fewer reservations than for the patient in case 1. This patient has an approximate 18% to 20% risk of regional lymph node involvement, which is more predictive of outcome than are the characteristics of the primary tumor. I would recommend that SLN biopsy be performed. The only instance in which I would not recommend the biopsy is if the patient had substantial medical co-morbidities that were more serious than a positive lymph node would be, which is clearly not the case in this otherwise healthy 46-year-old patient. Another consideration is that this patient is functioning at a fairly high level and would likely want to know how serious the melanoma is.

Dr Berger [TJU]: I would also definitely do SLN biopsy, which I do for most patients with melanomas > 0.75 cm. The number of mitoses reported for this patient makes the need for SLN biopsy even clearer.

Dr Mastrangelo [TJU]: I would recommend SLN biopsy based upon the probability of there being disease in those lymph nodes due to the thickness of the tumor and the number of mitoses.

Dr O'Grady [UCSD]: We generally refer patients such as this one to our surgical specialists to perform the excision, especially if SLN biopsy is indicated, as I believe it would be for this patient.

Dr McClay [UCSD]: I also agree with Dr O'Grady's treatment plan. This patient has a melanoma with a mitotic index of 26. From my perspective, that's a fairly poor prognostic factor and I would definitely proceed with SLN biopsy.

Surgical Margins for Intermediate-Thickness Melanoma

As previously described (see page 5), randomized clinical trials and many years of experience have indicated that an excision margin of 2 cm around the visible edge of a melanoma (or its biopsy scar) are as effective as wider margins in providing local control for primary melanomas thicker than 1 mm. Unless the primary site was located in an area where a 2 cm margin would be impractical to obtain, such as on the head and neck or the hands or feet, this is the excision margin recommended by current practice guidelines, and the margin we would recommend for a patient such as the one in this case presentation. For a primary tumor located on the back, as in this case, primary closure would be expected in almost every case. On the extremities, where skin grafting is required more frequently, we frequently employ full-thickness grafts using skin harvested from the sentinel node biopsy site to eliminate the need for an additional skin graft donor site.

SLN Biopsy in the Management of Intermediate-Thickness Melanoma

While the clinical utility of SLN biopsy for patients with thin melanomas remains debatable, as discussed in case 1, it is routinely recommended for detecting occult regional node metastasis in patients with intermediate-thickness primary melanomas. In this setting, SLN biopsy has a central role in determining prognosis, identifying patients who would benefit from regional lymphadenectomy and/or adjuvant therapy, and even a potential effect on survival when positive nodes are found. The Multicenter Selective Lymphadenectomy Trial (MSLT-I) randomized patients with intermediate-thickness melanomas (defined for the purposes of that study as Breslow thickness 1.2 to 3.5 mm) to either SLN biopsy (n = 769), with immediate lymphadenectomy for patients with positive SLNs, or to nodal observation (n = 500) with subsequent therapeutic node dissection if abnormal nodes became evident clinically or on imaging studies. In the patients randomized to SLN biopsy, the presence of metastasis in the sentinel node was the most important prognostic factor. Among patients with nodal metastases, the 5-year survival rate was higher for those with sentinel node biopsy detected metastases, who underwent immediate treatment.
lymphadenectomy, compared with those in whom lymphadenectomy was carried out when metastases became clinically detectable. However, for the entire group of patients with both positive and negative sentinel nodes, there was no evidence that sentinel node biopsy itself increased overall survival – as would be expected for a staging procedure.\textsuperscript{4,5}

In our practice, sentinel node biopsy is routinely offered to patients with intermediate-thickness melanoma who are considered healthy enough to safely undergo general anesthesia, as with the patient in this case presentation. Patients with significant co-morbidities undergo wide excision of their primary melanoma under local anesthesia and the lymph nodes are followed clinically, and where appropriate with ultrasonography as well.

References

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**Q** Would the pre-surgical workup for this patient differ from the workup for a patient with a thinner lesion, such as in case number 1?

**Dr Coit [MSK]:** Finding occult distant metastatic disease in the absence of a positive node is unlikely. So, I would not recommend cross-sectional body imaging for this patient, nor would I recommend it routinely for patients with a similar presentation. Tests necessary to ensure the safety of the anesthetic procedure would, of course, be performed. At MSKCC, these would include a chest x-ray, an EKG, a CBC, and clotting studies.

**Dr Berger [TJU]:** For work-up, I certainly would do liver function tests, LDH measurements, a hemogram, and chest x-ray. I’d also be more inclined to do cross-sectional imaging, based on how the lesion looks.

**Dr Mastrangelo [TJU]:** I would be very inclined to do a more extensive metastatic survey, in addition to the routine laboratory tests. I would do CT scans of the chest, abdomen, and pelvis, with and without contrast.

**Dr Berger [TJU]:** I had recommended a cross-sectional CT previously, so I wouldn’t do any other staging work up until after the lymph node results were known.

**Dr Easter [UCSD]:** I prefer to perform imaging studies of the nodes before the day of surgery. A CT scan with contrast of the chest, abdomen, and pelvis would be done beforehand. LDH and alkaline phosphatase would be measured; bone scanning or MRI would be unnecessary, in my opinion.

At UCSD, there are clinical trials investigating a new tracer that has a faster transit time and a longer in-node time. We are now using that tracer clinically. Before surgery, I would participate in a multidisciplinary discussion regarding clinical trials that may later become relevant. Future participation in a clinical trial can influence early treatment decisions.

**Dr Messina:** This patient had a wide excision with 2 cm margins and SLN biopsy of the ipsilateral groin. Very similar to case 1, two inguinal nodes were removed, both of which were hot and blue. The lymphoscintigram (Figure 2-3) shows drainage from the lateral back area into the inguinal region. Wide excision showed a scar consistent with the previous biopsy site. No residual melanocytic proliferation was found, and all margins were negative. A photomicrograph of the sentinel lymph node is shown in Figure 2-4. Low-power magnification of the lymph node appeared unremarkable. However, when using S-100 immunostaining (Figure 2-5), there are a number of positively staining cells seen indicated in the circle. The most numerous are single, lightly-staining cells. The highlighted area within the circle indicates where the strongly staining cells clumped. Higher power magnification of this area (Figure 2-6) reveals positively staining cells, both in clumps and singly. Last, Figure 2-7 is a high-powered hematoxylin and eosin (H&E) stain of one of those clumps, showing atypical epithelioid cells diagnostic for metastatic melanoma.

**Q** Given this patient’s pathology findings, would CLND and/or adjuvant treatment be advisable?

**Dr Coit [MSK]:** At this point, we would obtain a workup for this patient, who is at significantly higher risk for distant failure than the patient discussed in case 1. If no other disease were found, this patient would have an approximate 30% to 40% risk of systemic failure within the next 4 years. Although the yield of cross-sectional body imaging is very low for patients such as this one, the tests would be done to establish a baseline for future comparison. A PET scan and a noncontrast CT scan of the chest would also be performed. Because this patient is a pilot, she would require an MRI of her brain to have her pilot license renewed. That would be done, as well, so that she could continue to work.

With regard to CLND, this patient is at an approximately 15% to 20% higher risk for regional nodal failure. I would discuss the options with her, informing her of what is known and not known regarding CLND. The decision regarding CLND for this patient is difficult, because the nodes in question are in the groin, not the axilla,
and groin dissection is associated with a high risk of long-term lymphedema. Nonetheless, this patient has a high-risk melanoma, and I expect that the strategy would be more in favor of CLND than against it, based on the likelihood of residual disease and the high risk of recurrence. My inclination would be to do everything that might help, rather than doing only what has been conclusively proven to help.

At Memorial Sloan-Kettering Cancer Center, this would be primarily an inguinal dissection. In the absence of PET or CT evidence of pelvic lymphadenopathy, surgery would not include pelvic lymph node dissection. We routinely sample the Node of Cloquet during the inguinal lymph node dissection in patients who are clinically negative in the deep pelvis. If that node is positive, however, we would do a pelvic node dissection. We would not do an elective pelvic node dissection, in the absence of a specific indication to do so.

The Node of Cloquet is as much a concept as an anatomic reality. We think of the groin as having a femoral compartment and a deep pelvic or iliac/obturator compartment. The Node of Cloquet is the lymph node that lies in the femoral canal, just medial to the femoral vein, and seems to be the bridging node between these two basins. If the Node of Cloquet is negative, the likelihood of deep pelvic nodal involvement is less than 3%; if positive, the likelihood of deep nodal involvement approaches 30%. At MSKCC, we assess the Node of Cloquet in cases of positive SLNs as an indicator of whether a pelvic node dissection is necessary.

**Dr. Sondak:** If the Node of Cloquet were clinically uninvolved at the time of surgery, would you do a frozen section of the sample and wait for the pathology report before concluding the surgery? If the final pathology report found that the node was positive, would you go back and perform the pelvic node dissection?

**Dr. Coit [MSK]:** Sampling the Node of Cloquet is one of the few instances in which we do an intraoperative frozen section assessment. Although it is not a perfect indicator, it’s far easier on the patient to do the pelvic node dissection under the same anesthesia when

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**Figure 2-4.** Low-power view of the sentinel node reveals normal nodal architecture (H&E, 50x).

**Figure 2-5.** Immunohistochemical staining with S-100 antibody highlights an area suspicious for metastatic disease (100x).

**Figure 2-6.** On higher power, S-100-positive aggregates of cells can be seen amidst a background of single S-100-positive interdigitating reticulum cells (200x).

**Figure 2-7.** A higher power view of the H&E section of the lymph node identified on the S-100 stain shows a clump of malignant pigmented cells, diagnostic of metastatic melanoma (400x).

Source: Photomicrographs provided by Jane Messina, MD
the node is positive. We prepare the patient for the possibility of a deep node dissection, based upon examination of frozen sections of the Node of Cloquet. If the node were found to have disease after the surgery was completed, we would recommend a pelvic node dissection as a second procedure, although the impact of further node dissection on outcome has not yet been proven.

Dr Wolchok [MSK]: Regarding adjuvant therapy, I think the options remain the same as in case number 1. Since this patient has a high quality of life (QOL) and a very demanding job, the potential adverse effects of high-dose IFN on QOL must be taken into account. This patient probably would be unable to work for much, if not all, of the year during which high-dose IFN treatment would be given. On the other hand, this young, active patient should be thoroughly informed of the risks and benefits of standard therapy.

Dr Berger [TJU]: I certainly would recommend a complete inguinal lymph node dissection, despite there being very minimal disease in the node. For a microscopically positive node, I would do only a superficial lymph node dissection and would not immediately dissect the pelvic lymph nodes. The latter would depend on the volume of disease found at the completion superficial dissection.

Dr Mastrangelo [TJU]: I would recommend that this patient have a CLND. The metastases are multifocal, indicating more than one metastatic seeding of this lymph node, and increasing the likelihood that more disease will be found. Regarding adjuvant treatment, I believe that the toxicity of high-dose IFN-α outweighs its therapeutic benefit. My preference would be to enroll this patient in a trial of adjuvant immunologic treatment, if one were available.

Dr McClay [UCSD]: After the finding of positive lymph nodes in this patient, PET, CT, and MRI studies would be performed to better determine disease status.

Dr Easter [UCSD]: This patient has real micrometastatic disease. The justification for lymph node dissection to prevent regional recurrence is there. If you find involved lymph nodes at the highest level of the superficial groin dissection, some surgeons would advocate a deep groin and pelvic lymph node dissection. While these procedures do not extend survival, they will more accurately stage the patient and determine if there are more nodes involved.

Dr McClay [UCSD]: Regarding adjuvant treatment, this patient has a greater volume of disease than the patient in case study 1 patient, albeit still small. I believe that CLND would be advisable for this patient.

Dr Linson [UCSD]: Adjuvant RT can increase the likelihood of patients developing lymphedema, which we know to be quite troublesome. I would consider adjuvant RT for those patients who have been shown to have high rates of nodal basin failure, principally patients with extracapsular extension. More than four involved nodes would also make the patient a candidate for adjuvant RT. Obviously, if the surgery proves difficult or disease was left behind, that is another instance in which adjuvant RT would be advisable.

Dr Sondak: Would this patient be a candidate for investigational therapy?

Nurse Roman [MSK]: We would have the same discussion regarding investigational therapeutic vaccine trials with this patient, regardless of her specific category of stage III disease.

The Role of Preoperative Blood Tests and Imaging Studies

Although this patient is at somewhat greater risk of eventually developing distant metastases than the patient in case presentation 1 (based on the greater Breslow thickness and the higher mitotic rate), the likelihood of finding detectable evidence of metastases on either blood tests or imaging studies is still low, and false negative results would be commonplace. Therefore, we would not be inclined to recommend blood tests or imaging studies for this patient except as needed to facilitate safe conduct of surgery. After the completion of and recovery from surgery, imaging studies may be indicated prior to initiating adjuvant therapy or as a requirement of entry into a clinical trial. In most cases, any such studies obtained prior to surgery would need to be repeated for these purposes – a further reason to defer imaging until after surgery is complete. As noted in the discussion, this patient’s occupation (commercial airline pilot) may carry with it a requirement for additional imaging (such as a brain MRI to exclude even the remote possibility of brain metastases), and such patient-specific needs should always be considered.

Completion Lymph Node Dissection (CLND) in the Management of Sentinel Node Positive Intermediate-Thickness Melanoma

This patient likely has a higher risk of encountering identifiable metastases in non-sentinel nodes than the patient in case #1, again based on the thicker primary with its higher mitotic rate. Still, in the majority of cases histologic examination of the dissection specimen reveals no involved non-sentinel nodes. Complicating the decision-making in this case is the nature of patient’s job: a commercial pilot works in an environment conducive to the development of post-lymphadenectomy lymphedema, and this complication would likely limit her ability to function. Hence, even postponing inguinal
node dissection for a few years might be to her advantage if it was not associated with a significant penalty in terms of the oncologic outcome. Unfortunately, specific data on any of these points—the frequency with which positive non-sentinel nodes would be anticipated, the exact incidence of lymphedema, and the consequences of delaying lymphadenectomy if there is residual nodal disease—are lacking, at least to the level we would like to have to counsel a patient such as this. Because of that, we would discuss all these aspects—focusing particular attention on the long-term risks of inguinal lymphadenectomy and the possibility that side effects could be more severe if the patient suffers a nodal recurrence—and indicate that our recommendation is for completion node dissection. We would also discuss the option of participating in the MSLT-2 randomized trial comparing lymphadenectomy to observation with serial ultrasonography (see case presentation #1). Patients are always free, however, to choose whether to enter a clinical trial and even whether to accept physician’s recommendations. Certainly, in a case such as this one, we would work with the patient to define the best management strategy we could offer that would be acceptable to the patient.

When is pelvic node dissection indicated in inguinal node-positive melanoma?

An interesting sidelight to the current case presentation is the question of whether dissection of the pelvic nodes (particularly the external iliac and obturator nodes) should be included in the lymphadenectomy procedure. Some clinicians never advocate pelvic node dissection in the absence of radiologic evidence of involvement, fearing prohibitive morbidity will result from the removal of the pelvic nodes. Meanwhile, others advocate intraoperative evaluation of Cloquet’s node, with pelvic node dissection for those with identified metastases in that “transitional” node situated at the level of the inguinal ligament. The data supporting either of these positions are remarkably limited: there is no clear proof that lymphedema rates are dramatically higher after ilioinguinal dissection than after inguinal dissection only; and the positive and negative predictive value of Cloquet’s node (which by the way has been variously defined by different surgeons) is very poor.

Patients undergoing sentinel node biopsy provide another alternative for determining whether pelvic node dissection might be indicated: evaluation of the preoperative lymphoscintigraphy study to look for evidence of through transit of tracer into the pelvic nodes. In rare cases, we have seen evidence of primary drainage from cutaneous melanomas directly into sentinel nodes in the pelvis, and we consider this an indication for pelvic sentinel node biopsy. Far more often, however, we see one of two patterns associated with in-guinal drainage on lymphoscintigraphy: drainage exclusively to one or more nodes in the groin with no evidence of tracer in the pelvis (exemplified by the scan shown in Figure 1-4, case presentation #1); or drainage to nodes in the groin with faint, second-echelon drainage into the pelvis (as seen in this case on the lateral image in Figure 2-3). In cases such as these, our data suggests that the risk of microscopic involvement of the pelvic nodes is increased, and we have been recommending concomitant external iliac and obturator node dissection at the time of completion inguinal lymphadenectomy. This strategy has now been supported by others as well. Importantly, in our experience, while hospital stay after ilioinguinal lymphadenectomy is generally 1 or 2 days longer than after inguinal lymphadenectomy (where patients are usually discharged on the first postoperative day), long-term lymphedema rates have not been identifiably higher with the inclusion of the pelvic nodes. In fact, prospective data from the MSLT-1 trial indicated that the lymphedema rates for inguinal and ilioinguinal node dissections were the same. This trial also found a dramatically lower rate of lymphedema when groin dissections—whether superficial only or superficial and deep—were done for positive sentinel nodes than when they were done for clinically evident disease.

Regional and systemic adjuvant therapy for intermediate-thickness, sentinel node positive melanoma

We do not believe radiation therapy to the nodal basin offers an acceptable alternative to completion lymphadenectomy in patients with a positive sentinel node biopsy, although this strategy has been advocated for patients with positive nodes in the neck. We reserve postoperative radiation therapy for patients considered to be at high risk of nodal basin failure after lymphadenectomy, and use radiation more selectively in the inguinal region than in the neck or the axilla. In general, patients with at least 4 involved nodes and/or the presence of extracapsular extension are considered candidates for postoperative nodal radiation, which is integrated with adjuvant systemic therapy when administered. In the current case, unless a completion lymphadenectomy showed multiple additional involved nodes and extracapsular extension (a highly unlikely scenario given the sentinel node biopsy findings), we would not recommend adjuvant radiation therapy.

All of the considerations regarding adjuvant systemic therapy that were made in case presentation #1 certainly apply to this patient, with the realization that the 10-year risk of death is clearly higher than for the first patient. Based on the MSLT-1 randomized trial, this patient’s estimated 5-year relapse-free survival rate would be 53.4±4.9% (which is about the same as the 10-year relapse-free survival es-
timate for case #1), but the 5-year melanoma-specific survival rate is much lower than the patient in case #1: 72.3±4.6%. Faced with these risks and informed of the benefits and toxicities of therapy, many of our patients choose adjuvant high-dose interferon. Others choose to enroll on investigational trials, when available, and this is always encouraged. Of note, we consider decisions about adjuvant systemic therapy to be relatively independent of decisions about regional treatment of the lymph nodes. So, for patients who do not undergo completion lymphadenectomy – either because of patient refusal or by virtue of randomization on a clinical trial – we recommend adjuvant systemic therapy using identical criteria to those employed for patients after node dissection.

References:

Dr Sondak: The patient refused to undergo the recommended CLND and was unwilling to enter a clinical trial, because doing so might have resulted in randomization to surgery.

Would you now order additional workup for this patient—specifically, an ultrasound of the regional node basin—and what should this patient’s follow-up schedule be?

Dr Coit [MSK]: After a discussion of the pros and cons of CLND, if this patient chose not to have it performed she should understand that she is, in essence, in the experimental arm of the MSLT 2 clinical trial, which is ongoing and designed to determine whether SLN-positive patients should undergo CLND. I would inform the patient that she is at significant risk for regional nodal failure.

At Memorial Sloan Kettering Cancer Center, the patient’s baseline cross-sectional imaging would be available. We are also now starting to use ultrasound of the regional lymph node basin to supplement our physical exam. Our ultrasonographers are currently perfecting this technique, which is already commonly used in Europe. We would perform an ultrasound every 3 to 6 months on patients such as this one. A PET scan and noncontrast CT scan would be done once a year. She would have a follow-up examination every 3 months for the first 2 years, every 4 months during year 3, every 6 months for the next 2 years, and yearly thereafter, assuming that there is no recurrence. She also would be taught how to examine her own lymph nodes.

Dr Berger [TJU]: This patient would need to be examined every 3 months for the first year, with particular attention to ultrasound imaging of her inguinal node basin to determine if she is developing lymphadenopathy. I would recommend cross-sectional imaging at least every 3 to 6 months, every 3 months would be preferable for this patient who chose not to have CLND.

Dr Mastrangelo [TJU]: This patient should undergo ultrasonographic examination in her clinician’s office at each visit. In the presence of one positive SLN, there is a high probability of recurrent disease at related sites. I would examine the lymph nodes with ultrasound every 3 months for 2 years. I would limit CT scans to once a year, and obtain a chest x-ray, a hemogram, a liver function panel, and LDH measurement on a regular basis. Regarding adjuvant therapy for this patient, we’re limited basically to discussing IFN. Whether this patient, who refused CLND, would be eligible for a clinical trial of adjuvant treatment is questionable.

Nurse Laudadio [TJU]: That’s correct, Dr Mastrangelo. Few clinical trials of adjuvant therapy are open to patients who have not had CLND. We would monitor this patient and alert her if she were eligible for a vaccine therapy or other adjuvant treatment trial.
Follow-Up in the Management of Intermediate Thickness Melanoma

Follow-up for surgically treated melanoma patients is aimed primarily at the detection of disease recurrences or new primary skin cancers that can potentially be curatively treated. Outside of a clinical trial, the management of the sentinel node-positive basin in a patient who refuses completion lymphadenectomy remains undefined. Based on the design of the MSLT-2 trial, which incorporates nodal ultrasound every 4 months for the initial several years and every 6 months thereafter, we have employed a similar strategy in our patients. There are clear limitations to this approach: changes in the appearance of lymph nodes are common over the course of follow-up, and patients often require multiple ultrasound-guided FNA biopsies to exclude the interim development of metastatic disease. Conversely, we have had patients under careful ultrasound follow-up present with obvious palpable nodal disease that developed between scans. Multiple grossly positive nodes have been encountered at therapeutic lymphadenectomy in several of our patients followed with ultrasonography. Hence, careful clinical surveillance is an important component of the management plan for patients choosing to forgo surgical staging and/or dissection of the regional nodes.

Regardless of the management of the nodes, patients with a surgically treated malignant melanoma require follow-up evaluation of their skin, since their risk of developing a second cutaneous melanoma, as well as nonmelanoma skin cancer, is significantly higher than in the general population.

Local and in transit recurrence (disease recurring between the primary site and the regional nodal basin) should also be looked for as part of follow-up evaluations. Depending on the stage of the melanoma and whether the patient is on a clinical trial, as well as where they live in relationship to the Cancer Center, at Moffitt the responsibility for follow-up of the melanoma patient is shared among the surgical oncologist, medical oncologist, dermatologist and primary care physician. For a patient such as the one in this case presentation, who has chosen to forego completion dissection, the surgical oncologist plays a particularly central role in the follow-up scheme.

Routine laboratory tests—including LDH—and chest radiographs have not been shown to be beneficial in screening for visceral disease in asymptomatic patients.

Moreover, in most cases the detection of metastatic disease a few weeks or months before it becomes symptomatic or detectable on physical examination offers little benefit to the patient with stage IV disease. New follow-up strategies need to be evaluated to see if the percentage of patients who are diagnosed with potentially resectable stage IV melanoma can be increased, and if doing so results in improved long-term outcomes.

References:
4. Morton RL, Craig JC, Thompson JF. The role of surveillance chest x-rays in the follow-up of high-risk melanoma patients.

If the patient opted for adjuvant treatment and developed an inguinal nodal recurrence during treatment, how would you address that development?

Dr Wolchok [MSK]: If the patient develops a nodal recurrence during treatment, which sometimes happens regardless of the choice of therapy, I reassess the patient with systemic cross-sectional imaging, making sure that there are no metastases outside the regional basin, and then refer the patient for surgical consultation.

Dr Coit [MSK]: Yes, if the patient develops nodal recurrence, she would undergo a complete set of imaging studies with particular attention to the pelvic nodes, because this would be an inguinal nodal recurrence. If she had no evidence of distant disease, I would recommend a therapeutic groin dissection. In the absence of significant extranodal disease, a discussion of adjuvant therapy would be the next step, particularly if she had previously elected not to have it.

Dr Easter [UCSD]: If the patient developed a nodal recurrence during adjuvant treatment, I would certainly resect the tumor and investigate a vaccine treatment. If the patient were receiving immunologic therapy and the recurrence occurred relatively early, I probably wouldn’t change the treatment. Depending on the patient’s immune system, an immunologic response could take 3 or 4 months. If the patient were receiving chemotherapy and had an early recurrence, I would consider that a treatment failure and move on to another treatment modality or to enrollment in a clinical trial.

Nurse Petzinger [UCSD]: If adjuvant chemotherapy is given, we usually start with four cycles given every 4 weeks, after the patient has healed from the surgery. Platinum, as everyone knows, is associated with a high incidence of nausea. Thankfully, we have so many new drugs that counter the nausea that patients are able to tolerate four cycles much better than in the past. Very few experience severe adverse effects.

Dr Sondak: As you may be aware, European clinicians who treat melanoma continue adjuvant therapy, despite a regional or local re-
Recurrence During Adjuvant Therapy

As previously stated, recurrent melanoma occurs in approximately half of patients with thin or intermediate-thickness melanomas and positive nodes within the first 10 years after surgery. In the MSLT-1 trial, the median time to nodal failure for patients with intermediate-thickness melanomas treated with surgery alone who did recur in the nodes was only 16 months. Thus, recurrent melanoma during adjuvant therapy is not an uncommon clinical scenario.

Surgery remains the first-line treatment for local and regional recurrences. Recurrences in nodal basins and other soft tissue sites are best confirmed with fine needle aspiration, as excisional biopsy can make subsequent definitive surgery more complicated. We believe that virtually all patients with a history of melanoma who present with a palpable lymph node suspicious for malignancy should have FNA attempted as the first diagnostic modality, rather than proceeding straight to excisional biopsy. Because patients who have recurred at a local/regional site are at significant risk of having radiographically detectable distant metastatic disease, a chest x-ray and blood LDH level are performed at the time of FNA, and depending on the site of the recurrence and the nature of the treatment required to deal with it, we usually order a PET/CT fusion scan and brain MRI, sometimes along with a non-contrast CT of the chest, prior to definitive surgical treatment of the recurrence. Recurrence in the inguinal basin would, in our hands, generally be treated by ilioinguinal (superficial and deep) node dissection because of the significant risk of finding histologically positive pelvic nodes.

If a potentially resectable recurrence such as a nodal recurrence occurs during adjuvant therapy, that therapy is interrupted while the restaging evaluation and definitive surgical management is carried out. The decision to resume the same adjuvant therapy is individualized and made after careful consideration of the toxicity of therapy to date and the patient’s wishes. In general, for immunologically-based therapies such as adjuvant interferon or investigational vaccines, if the patient has been tolerating therapy satisfactorily we will resume the same therapy postoperatively after recovery from the effects of surgery. If tolerance of the adjuvant therapy has been problematic, therapy is usually permanently discontinued and the patient evaluated for possible enrollment in a clinical trial. While we virtually never employ adjuvant chemotherapy outside of the context of a clinical trial, we agree with the discussant who indicated that an recurrence during chemotherapy would generally be considered a treatment failure and that chemotherapy discontinued permanently at that point.

References:


2010 update: This patient, who declined both completion node dissection and adjuvant interferon, remains well without evidence of local, regional or distant recurrence five years after her sentinel lymph node biopsy.
Case Presentation 3: Unknown Primary Melanoma Presenting with Nodal Metastasis

Case Presentation
The patient is a 72-year-old grandmother with a 2-month history of a palpable mass in the right neck. The patient has no personal history of melanoma or of a regressing mole or removed skin lesion. Prior to being referred, fine needle aspiration (FNA) biopsy was performed and found to be positive for cells consistent with metastatic melanoma. Results of immunohistochemistry performed on a cell block from this aspirate are shown in Table 3-1. Photomicrographs from this aspirate are shown in Figures 3-1 and 3-2. PET/CT scanning reveals one hypermetabolic lymph node in the right neck, and another one in the right axilla. A brain MRI performed at presentation was negative for CNS metastasis.

### Table 3-1

<table>
<thead>
<tr>
<th>Immunohistochemistry Report</th>
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<tr>
<td>Immunohistochemical stains with appropriate controls revealed:</td>
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<tr>
<td>S-100 ................. Positive</td>
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<tr>
<td>HMB-45 .............. Positive</td>
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<tr>
<td>Melan-A ............. Positive</td>
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<tr>
<td>Vimentin ............ Positive</td>
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<tr>
<td>CK 7 ................. Negative</td>
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<td>CK 20 ................. Negative</td>
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<td>TTF-1 ................. Negative</td>
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What additional workup is indicated for this patient, and how would you search for the patient’s primary tumor?

Dr O’Grady [UCSD]: The physical exam is always the first place to start, and the first thing that I do is a complete skin exam. A complete skin exam goes from the top of the scalp to the web spaces of the toes and the bottom of the feet. The exam includes looking at the perianal skin, the ear canals, the oral cavity, and eyelids—all of the places that do not normally get examined and are hard for the patient or the patient’s partner to notice. Also helpful is a complete skin exam using a Wood’s light, which allows detection of areas of hypopigmentation or depigmentation not evident under normal light. The Wood’s light exam can lead you to the area of the primary lesion.

Unfortunately, histologic examination of areas that are hypopigmented or depigmented usually reveals an area of postinflammatory pigment change, and the lesion, which is more than likely completely regressed, is usually not evident. So, you
have either a completely regressed primary or you have a primary lesion that is from a body site that cannot be seen under normal examination. The clinician must also consider the very rare instances in which melanomas arise in parenchymal organs. Even after rigorous examination, there is no way to know the origin of the primary tumor in some cases.

This patient’s findings are very interesting. At a recent conference here in San Diego, one of the cases presented was a very difficult in situ melanoma progressing to early-invasive melanoma that essentially masqueraded more as a lentigo, or solar-damaged skin. An accurate diagnosis of lentiginous lesions is difficult, because these lesions can skip and an area of what appears to be normal basilar hyperpigmentation will be seen. Another case from that conference involved a large-cell acanthoma in which the histologic changes occurred only in large keratinocytes, which can mimic squamous dysplasia. Accurate diagnosis requires sectioning specimens to be sure that an area of in situ melanocytic proliferation is not missed. This can be particularly difficult in older patients, who tend to have extensive dyschromia, for example solar lentigines, actinic keratoses, and hypopigmentation. These conditions can obscure or disguise melanocytic proliferations in the skin. For specimens from older or heavily sun-damaged patients—especially samples from the head, neck, or face—I either carefully examine deeper levels of the block or obtain immunohistochemistry stains to be sure that I'm not missing a subtle melanocytic proliferation. In certain cases, they can be very subtle and difficult to diagnose.

**Dr Sondak:** Would the biopsy of the suspect area, for example an area 1.0 to 1.5 cm, require complete excision or would a punch biopsy be sufficient?

**Dr O’Grady [UCSD]:** I'm not sure that excising the entire area would be productive. For an area that size, an incisional biopsy would, at least, allow examination of the breadth of the lesion. I'm not a great fan of punch biopsies, because the punches used are often too small; I would probably recommend an incision to sample the entire breadth of the lesion, and then examine it for changes.

**Dr Mastrangelo [TJU]:** I would limit the work-up for this patient to a history, a physical examination, and a Wood's lamp evaluation. Examination of the eyes, nasopharyngoscopy, upper endoscopy, and colonoscopies and other screening tests for this patient would not be worthwhile.

**Dr Berger [TJU]:** I would, of course, do a physical examination and some type of metastatic survey. I tend to favor the PET scan for patients with stage III melanoma.

**Dr Coit [MSK]:** As far as an additional workup for this patient with an unknown primary melanoma, I would not rely on her history alone. Examination with a Wood's light, with particular attention to the area of skin between the neck and the axilla, would be needed. Although some clinicians would refer this patient to an ophthalmologist for an eye exam, I would not. I do not believe the eye is a likely potential primary site for metastatic nodes in these locations. I would recommend a non-contrast CT scan of the chest, which is the most common site of visceral metastatic disease.

**Q** Would you recommend a radical neck dissection and/or axillary-node dissection for this patient?

**Dr Easter [UCSD]:** I would not recommend radical neck surgery for this patient. This is a patient for whom systemic, not regional, issues are paramount. I would do a selective node dissection to better stage the patient, if it affected the choice of systemic therapy. The surgeon must think two or three steps ahead. This conservative approach also applies to the axilla. I would do a Level I or II axillary dissection and avoid a Level III dissection, unless it influenced future systemic treatment options. If not, I would remove bulky disease only.

**Dr O’Grady [UCSD]:** I agree. I would ask that you be aggressive in removing all known disease. For this patient, radical neck dissection should be avoided in favor of removing any detectable local disease.

**Dr Mastrangelo [TJU]:** Surgery for head and neck cancer has diminished and RT has increased. I don’t think that that’s appropriate for melanoma of the head and neck, which, I believe, typically requires a more extensive operative procedure. Surgery for melanoma has to be definitive, since adjuvant treatments are generally ineffective.

**Dr Berger [TJU]:** Regarding surgical treatment, I would recommend that the patient undergo what I call “modified radical neck dissection,” in the absence of any metastatic disease. I typically do a thorough clean-out of levels II-V and tend to be aggressive toward the sternocleidomastoid muscle and jugular vein. In the absence of metastatic disease, this would give this patient a chance of cure.
Metastatic Melanoma

Metastatic melanoma presenting in the absence of a known primary – “unknown primary melanoma” – now accounts for about 3% of new patients presenting to multidisciplinary melanoma clinics.\textsuperscript{1,2,3} The first, and in most cases, most important step in evaluation is a thorough history and physical examination. In the history, we specifically inquire about any and all skin lesions that have been excised for biopsy or ablated (eg, with liquid nitrogen), regardless of the presumptive diagnosis. If a skin lesion has been biopsied from a region of skin potentially draining to the nodal site(s) involved by tumor, especially it was diagnosed originally as some type of benign or atypical nevus, we endeavor to obtain the original biopsy slides for review by our dermatopathologist. Occasionally, through the benefit of hindsight and by comparison to the cells seen in the regional node, a definitive diagnosis of the primary cutaneous melanoma can be made retrospectively. We also ask specifically about skin lesions that have changed or disappeared due to trauma or spontaneous regression, and have had a number of patients who gave a characteristic history of an irregular pigmented lesion consistent with melanoma that spontaneously regressed and disappeared over time. In some cases, the patients have been able to find old photographs that documented the presence of an obvious melanoma in a site that now appears unremarkable or slightly depigmented.\textsuperscript{4} Of course, physical examination should focus on areas that could harbor a primary melanoma that would be difficult for the patient to see, including the scalp, posterior neck and back, perineum and between the toes. Here again, particular attention is paid to examining the difficult-to-see areas that would be expected to drain to the node(s) known to be involved by melanoma.

Areas of regression which could be the remnant of a regressed primary are notoriously difficult to see, especially on heavily sun-damaged skin. To augment our evaluation of the unknown primary melanoma patient, once a thorough skin examination has been completed we take the patient to a darkened room for examination of the skin with a Wood’s lamp (“black light”). Areas of depigmentation stand out very clearly under this illumination, and a surgical marker is used to encircle any areas for later inspection under normal lighting conditions. Particular attention is paid to irregular areas of depigmentation and/or those with adjacent areas of residual pigmentation, and if these are seen excisional or incisional biopsy is carried out. When incisional biopsy is performed, we prefer a larger-diameter (6 mm) punch biopsy. Good communication with the dermatopathologist is always helpful when a punch biopsy is performed in lieu of complete excision, so that it is clear the nature of the lesion being sampled and the extent of residual abnormality visible after the punch. In the absence of signs or symptoms pointing to some type of occult non-cutaneous primary, we do not carry out any specialized testing nor do we routinely refer the patient to specialists such as ophthalmologists, otolaryngologists or gynecologists for additional evaluation. When dealing with unknown primary melanoma in the inguinal or pelvic lymph nodes, where a vulvovaginal or anorectal primary is a consideration, the history includes asking about perineal procedures such as hemorrhoidectomies or ablation of “genital warts” that could have represented destruction of the primary tumor. In addition to the routine physical examination of these areas, at the time of surgery we often make it a point to conduct an examination under anesthesia to evaluate the genital region during placement of the Foley catheter and repeat a digital rectal examination and if needed anoscopy. For unknown primary melanomas presenting with cervical nodal metastases, intraoperative evaluation of the upper aerodigestive tract can be done during the time of intubation, so it is important to alert the anesthesiologist to this possibility and modify the routine intubation approach if necessary.

In addition to the possibility that the primary cutaneous tumor has regressed or been removed or destroyed, the theoretical possibility exists that melanoma can arise from melanocytes located within the lymph node itself (“nodal nevus” cells) or in visceral organs. Until recently, there has been no conclusive support for this possibility. However, molecular evaluation of a small series of “unknown primary” melanomas presenting as metastases to the GI tract indicated that all four cases harbored a genetic translocation characteristic of primary clear cell sarcoma, namely the EWS/ATF1 translocation.\textsuperscript{5} Whether similar results will be seen for nodal lesions previously characterized as unknown primary melanomas remains to be seen. At present, however, this molecular distinction conveys no known therapeutic distinction and treatment decisions are not based on such analyses.

Indeed, the primary management of any unknown primary melanoma is identical to that for a known primary melanoma of the same stage and location. So for a patient presenting with palpably involved nodes in the neck, regardless of the presence or absence of a known cutaneous primary, surgical extirpation in the form of some type of definitive cervical lymphadenectomy is indicated. A full “radical neck dissection”, which includes routine removal of the sternocleidomastoid muscle and the jugular vein and sacrifice of the spinal accessory nerve (cranial nerve XI), is rarely if ever indicated in melanoma. In most cases, a “modified radical neck dissection” that spares the sternocleidomastoid (which is sometimes divided and reapproximated to facilitate node clearance) and the jugular vein is performed; the spinal accessory nerve is taken only if involved by or closely approximated to tumor – which unfortunately is a frequent occurrence. “Selective neck dissection” refers to modified neck dissections that are further altered to preserve some normal-
appearing levels of the cervical nodes deemed very unlikely to harbor occult metastases. For example, melanomas of the upper back or chest would be considered very unlikely to involve the submental nodes even if supraclavicular or low neck nodes were obviously abnormal. In the absence of a known primary, however, these judgements are difficult if not impossible to make, and the small added morbidity of the complete dissection appear to be well-justified. Modified radical neck dissection encompassing all levels of the neck on the affected side (ie, levels I-V) is the procedure that was performed to address the biopsy-proven cervical node involvement in this case presentation.

A similarly aggressive approach is taken to the axilla, given the finding of a hypermetabolic node ipsilateral to the biopsy-proven neck disease. The diagnosis of metastatic melanoma can be substantiated preoperatively by ultrasound-guided FNA or intraoperatively by frozen section analysis as part of a one-stage procedure, as was done in this case. The standard axillary dissection for metastatic melanoma – whether documented in a normal-appearing sentinel node or in an obviously abnormal enlarged node – involves at a minimum complete dissection of levels I and II of the axilla, a more thorough dissection than is often done for micrometastatic breast cancer, for example.6 We make an effort to remove potentially node-bearing tissue superior to the axillary vein, which can harbor micrometastases from melanoma but is rarely involved by breast cancer. We also routinely carry the dissection into level III (medial to the medial edge of the pectoralis muscle) but do not divide the pectoralis minor muscle routinely unless needed to excise palpable adenopathy in level III. Dissecting level III without dividing the pectoralis minor requires a stout individual (in stamina at least, if not stature) to provide retraction, albeit for a relatively short period of time, as we eschew mechanical retractors in this setting. We would never hesitate to divide the pectoralis minor if required to clear out an involved level III node, as the morbidity is modest and far superior to uncontrolled disease high in the axilla! Even in an elderly patient, as in the case presentation, both an axillary and a modified radical neck dissection of the extents described can be carried out during the same general anesthetic, with an anticipated one or two day hospital stay.

References:

Dr Zager: This patient did have a presurgical evaluation using a Wood’s lamp, which revealed an area of depigmentation on the posterior right shoulder. The patient underwent excision of that site, along with modified radical neck and level I-III axillary lymph node dissection. Figure 3-3 is a photomicrograph of one of the cervical nodes. The node is almost completely replaced by the sheet-like cells of melanoma. A residual rim of normal lymph node can be seen on the right side of the photomicrograph, which is the more purple area.

The arrow in Figure 3-4 indicates the edge of the lymph node capsule, and tumor extension beyond the capsule into the perinodal fat is evident. The final pathology report identified that the

Figure 3-3. Lymph node demonstrates nodule of malignant nonpigmented cells, with residual rim of lymphoid tissue at edge (H&E, 100x).

Source: Photomicrograph provided by Jane Messina, MD
Given these findings, would you recommend postoperative adjuvant radiation therapy for this patient? If so, which sites should be irradiated?

**Dr Linson (UCSD):** Extracapsular extension increases the risk of regional lymph node failure, and disease extension into cervical lymph nodes, in particular, is associated with a higher likelihood of failure than disease in axillary or groin nodes. Also, the probability of failure in the nodal basin increases in proportion to the area of involvement in the lymph node. For this patient, hypofractionated RT, perhaps 24 to 30 Gray in two fractions per week over a 3- to 4-week period, would be helpful. Patients can tolerate such a regimen quite well. Intensity-modulated radiation therapy (IMRT) allows better sculpting of the dose, confining the radiation to the region at risk and avoiding nearby critical areas.

**Dr Berger (TJU):** I wouldn’t radiate this patient’s axilla, despite the positive finding in two nodes and extension beyond the capsule. The patient already has had a radical excision. If you radiate her axilla, lymphedema of her arm is a virtual certainty. I would not subject her to that at this point, but radiating her lymphedema and reduced mobility of the shoulder. But this is a fairly regionally aggressive melanoma with extracapsular extension, which, I believe, justifies adjuvant RT to both the cervical and axillary areas. High-dose IFN following RT and entry into a vaccine trial are also possibilities for this patient.

**Dr Mastrangelo (TJU):** Adjuvant IFN would have very little impact on this patient, given the extent of her disease. My inclination would be to give this patient empiric systemic chemotherapy.

**Dr McClay (UCSD):** I would definitely offer this patient adjuvant therapy. I would encourage participation in an appropriate clinical trial, which is the generally favored option. For a high-risk, elderly patient such as this one, a clinical trial of adjuvant biochemotherapy may not be appropriate. If the patient did not want to participate in a clinical trial, I would recommend a course of tamoxifen and a platinum analog for four cycles.

**Figure 3-4. Lymph node capsule (arrow), demonstrating presence of tumor on both sides, indicating presence of extracapsular extension (H&E, 100x).**

Source: Photomicrograph provided by Jane Messina, MD

**Dr Zager (continued):**

Should depigmented area was a solar lentigo with features of large cell acanthoma. Thus, there was no evidence that this represented the primary lesion. In Levels I through III of the cervical lymph nodes, 0 of 9 nodes showed metastatic melanoma; in Levels IV-V, 3 of 13 nodes contained metastatic melanoma with extracapsular extension. Two of 18 nodes in the axilla were positive for metastatic melanoma, also with extracapsular extension.

Q Would adjuvant systemic therapy be indicated for this patient and, if so, which treatment regimen would you prescribe?

**Dr Mastrangelo (TJU):** Adjuvant IFN would have very little impact on this patient, given the extent of her disease. My inclination would be to give this patient empiric systemic chemotherapy.

**Dr McClay (UCSD):** I would definitely offer this patient adjuvant therapy. I would encourage participation in an appropriate clinical trial, which is the generally favored option. For a high-risk, elderly patient such as this one, a clinical trial of adjuvant biochemotherapy may not be appropriate. If the patient did not want to participate in a clinical trial, I would recommend a course of tamoxifen and a platinum analog for four cycles.

**Nurse Petzinger (UCSD):** We’ve had extensive experience with biochemotherapy at UCSD. Patients come in daily for 5 consecutive days and receive platinum, IL-2, and IFN-α IV. The patients are thoroughly hydrated with at least 1.5 liters of fluid and are also given antiemetics. Although many patients develop fevers, the majority of patients can be managed on an outpatient basis. Whether this 72-year-old patient could tolerate such a regimen would first be discussed by all clinicians involved in her case.

**Dr Coit (MSK):** At MSKCC, our approach to patients with metastatic melanoma to two nodal basins, regardless of whether or not the primary site is known, is to recognize that they have a high likelihood of treatment failure. We have just recently begun offering such patients neoadjuvant treatment as part of a clinical trial. These patients may respond to the agents being tested, and this also may help to guide decisions about postoperative adjuvant systemic treatment.

We’ve recently completed a clinical trial of the cytotoxic alkylating agent temozolomide used adjuvantly. IFN has also been used as a neoadjuvant agent for patients such as this one—resectable, but at very high risk. We would offer this patient a trial of neoadjuvant therapy, treat to best response (which has ranged from early progression to complete histologic response), and then operate at the time of best response. If there were involvement of only one basin, the starting point would be therapeutic lymph node dissection; anything other than that would have to be considered experimental.

**Nurse Roman (MSK):** Patients who do not rapidly respond to either IFN or temozolomide usually want immediate surgery. They are afraid of delaying surgery while waiting for a response to systemic treatment.
Systemic Treatment of Malignant Melanoma

Indications for postoperative radiation to regional nodal basins have already been discussed (see page 16) and include four or more involved nodes and/or the presence of extracapsular extension. These are relative rather than absolute indications, and a number of factors play into the final decision whether or not to radiate a given nodal basin. In general terms, the morbidity of nodal basin irradiation gets higher as the basin gets lower, that is, it is least for cervical nodes, intermediate for axillary nodes, and most for inguinal and pelvic nodes. Thus, we are more likely to recommend postoperative radiation to a neck or axillary nodal basin than the groin. We are also somewhat less likely to recommend radiation to multiple nodal basins, especially in an elderly patient. Of course, patients who are at high risk of nodal basin failure are also at very high risk of systemic recurrence and regional recurrence outside the field that would normally be radiated (eg, in transit recurrence between the primary and the regional basin). These considerations limit the value of radiation to multiple nodal basins, especially in an elderly patient. Of course, patients who are at high risk of nodal basin failure are also at very high risk of systemic recurrence and regional recurrence outside the field that would normally be radiated (eg, in transit recurrence between the primary and the regional basin). These considerations limit the value of any regional treatment, including radiation, and need to be factored into treatment decisions. If a patient does manifest nodal basin recurrence and has not had irradiation to that basin, we routinely recommend it after resection of the recurrence since such patients are at extremely high risk of further regional failure.

Regarding adjuvant systemic therapy, the patient is clearly at high risk of distant failure as well as regional recurrence. It remains unclear whether adjuvant interferon is more effective in patients with microscopic or macroscopic nodal metastases (if there is a difference at all), but clearly the increased risk of relapse and death with palpable nodal disease means that, for the same relative risk reduction, the patient gains a greater absolute advantage with adjuvant therapy. Possibly arguing against adjuvant therapy is the patient’s age: older patients tend to value current quality of life more than future extension of life, which due to the natural progression of aging may be of lower quality than is currently the case. Increasingly, however, we are finding many of our older patients lead vigorous lifestyles and approach medical decision-making aggressively. Hence, we would approach the discussion regarding adjuvant high-dose interferon with this patient in a neutral way, without offering a firm recommendation for or against treatment. We would also discuss available investigational alternatives—some of which are potentially as aggressive as interferon, others of which might offer lesser toxicity. In the current case, after an extensive discussion and consultation with a medical oncologist, the patient elected to forego adjuvant systemic therapy.

Dr Zager: The patient refused adjuvant therapy and was monitored with serial CT scans of the neck, chest, and abdomen. During follow-up, the patient developed a new left lower lobe lung nodule, which was 1.5 cm in size and hypermetabolic on PET scan. No other evidence of disease was found.

Q: How would you evaluate and/or treat the lung nodule?

Dr Easter [UCSD]: Although surgery for metastases is usually ineffective, simple excision of isolated tumor metastases, whether they are in the abdomen, chest, or liver, can result in long-term benefits. If this 72-year-old patient were otherwise healthy and we wanted a definitive tissue diagnosis, I wouldn’t hesitate to offer a video-assisted thoracoscopic (VAT) wedge resection. Although this procedure is typically indicated for only a small number of patients with isolated lesions, it would result in palliation of any symptoms, a reliable diagnosis, and, potentially, long-term remission for this patient. One of the reasons that I favor this approach, when it’s reasonable from the patient’s perspective, is that it provides tissue to process for autologous vaccine and makes the patient eligible for a clinical trial.

Dr McClay [UCSD]: Yes, exactly. We’re fairly lucky here in San Diego, since we have Cyberknife treatments that have a high success rate for solitary lesions. I would not hesitate to refer this 72-year-old patient, even one with a poor performance status, to Dr Linson for possible Cyberknife treatment.

Dr Linson [UCSD]: Until recently, there would be very little I could offer these patients using conventional RT or even IMRT. Now, however, melanoma patients with brain metastases can do just as well as patients with metastatic breast or lung tumors. Cyberknife radiosurgery allows us to treat metastases as a moving target, whether the metastases are in the lung or anywhere else in the body. High-dose radiosurgery given in 3 or 4 fractions to patients with melanoma, or for any other solid tumor metastatic to the lung, can achieve local control in 85% to 90% of cases. For melanoma patients with limited, solitary pulmonary metastasis, the option of radiosurgery is now viable. Unlike standard RT, which would require 8 to 9 weeks to administer an equivalent dose, we can now administer high-dose radiosurgery over 3 to 4 days, with very limited morbidity and few adverse effects. If patients are not good surgical candidates or do not want surgery for whatever reason, we discuss this option with them.

Dr McClay [UCSD]: From my perspective as a medical oncologist, chemotherapy in this particular disease has been, historically, ineffective. But we have a number of different clinical trials of patients with metastatic disease that has been surgically resected or is unresectable. My first option, barring the Cyberknife or surgery, would be to offer this patient participation in a clinical trial. If no clinical trial is open to the patient and the patient is otherwise healthy, then I would consider treatment with systemic chemotherapy.

Dr Berger [TJU]: If it’s a peripheral lesion, it can certainly be excised via a VAT procedure, with relatively little morbidity. However, she will likely develop further disease, at some
Coit [MSK]: This is a woman at high risk for metastatic disease who has developed a visible pulmonary metastasis that was not present 8 months earlier. An alternative to immediate resection would be a brief interval of adjuvant systemic therapy, which has a significant potential to eradicate whatever micrometastases may be present. It is immediate treatment of systemic disease and establishes whether the disease isemo-sensitive. Most importantly, it allows us to determine whether this is the first and only metastasis or the first of many metastases.

Wolchok [MSK]: After the lung nodule has been found, the patient would be evaluated for resection. This would screen very carefully, including a brain MRI and also a high-resolution CT scan of the chest. I would not rely solely on the PET scan identification of this as a solitary metastasis. If there were no other signs of metastatic disease, I would refer this patient for a metastasectomy.

Zager: The patient had a wedge resection of the lung nodule. Pathology photomicrographs from that resection are shown in Figure 3-5, in which normal alveolar tissue can be seen at the upper right-hand portion of the figure. On the left-hand side, there’s a solid growth of cells which, at higher power (Figure 3-6), can be seen to be forming glands which dissect along the lines of the pre-existing alveoli. They are lined by plump atypical type II pneumocytes growing along and replacing alveolar septae, consistent with bronchioloalveolar carcinoma (H&E, 400x).

Q Would adjuvant therapy for this patient’s lung cancer be advisable?

Dr McClay [UCSD]: At this point, I would not offer the patient systemic chemotherapy. This very early primary lung cancer has been found serendipitously and, since only a modest resection of the particular tumor has been performed, I think RT to the area may be advisable.

Dr Linson [UCSD]: We know that patients are at a higher risk for local failure with VAT versus lobectomy. We could consider completion lobectomy. The location of the tumor is critical. I wouldn’t consider Cyberknife radiosurgery if the tumor was spread over a large portion of the lung, because the target would be too diffuse. We have done standard external beam RT in some instances. The risk of local failure in cases such as this one is approximately 15% to 20%, so I would discuss the risks with the patient. Should the patient fail over time, there is a chance for salvage Cyberknife radiosurgery, but she does have competing risk factors that would have to be considered.

Dr Easter [UCSD]: Finding the lung tumor early was fortunate. But a patient such as this one, with two primary tumors, would probably not be eligible for a clinical trial. I would individualize treatment for this 72-year-old patient, taking her preferences into account. For patients at risk of recurrent lung cancer or melanoma, additional surgery on the lung would be unlikely to help.

Dr Mastrangelo [TJU]: Regarding this patient’s lung nodule found during follow-up at 8 months, I would recommend systemic treatment, despite her age of 72 years. Of course, I would first consider any comorbidities and her general physical condition.

Dr Coit [MSK]: After adenocarcinoma with bronchoalveolar features was confirmed in this patient, I would refer her to a specialist in thoracic oncology to determine if adjuvant therapy would be advisable. Adjuvant therapy is a possibility, but I would likely not yet recommend chemotherapy. Since the primary lung tumor is still relatively small, I would elect to closely monitor it at this point.
Pulmonary Metastases

Pulmonary metastases are a very common site of disease recurrence in patients with melanoma. They may present with symptoms, but most often are found when asymptomatic, on routine chest radiographs or on screening scans such as PET or CT scans. Because they are so common, it is natural that our entire panel assumed the new abnormality seen on PET scan was a metastasis. The logical first step in this patient’s evaluation is a restaging workup to see if other metastases are identified. If the pulmonary nodule was first identified on chest x-ray, a PET/CT scan and brain MRI would be a logical next step. If the lung nodule was hypermetabolic on PET scanning and no other evidence of metastasis was seen, we would obtain a non-contrast chest CT to look for additional nodules too small or insufficiently FDG-avid to be seen on PET or the accompanying low-resolution CT scan. But this case illustrates an important principle of oncology: not every new nodule is a metastasis of the patient’s original malignancy. The differential here clearly includes a second primary cancer, and even some benign pulmonary nodules can show up as hypermetabolic on PET. Surgical resection is an important modality in the treatment of isolated pulmonary metastases or resectable primary lung cancers, and obviously will allow a definitive diagnosis to be established. Treatment with stereotactic radiosurgery is certainly an option, but would not yield a tissue diagnosis. Therefore, if the patient were a poor candidate for surgery and a nonoperative approach were selected, pretreatment biopsy of the lesion by image-guided FNA would be appropriate. Criteria for pulmonary metastasectomy include: (1) the patient being a good risk for surgical intervention; (2) control of the primary malignancy; (3) no other extra-pulmonary metastasis; and (4) completely resectable pulmonary lesions. The appropriate selection of candidates according to these criteria leads to an overall 5-year survival after pulmonary metastasectomy of about 30% to 40%. This is certainly far in excess of what could be expected from systemic therapy of any type, and we would not use systemic therapy for a patient like this with an isolated metastasis.

Finally, while adjuvant chemotherapy has been increasingly advocated for primary lung cancer, we strongly question whether this would materially decrease the patient’s risk of dying from metastatic melanoma. A patient who refused adjuvant therapy for her melanoma, such as the one in this case presentation, would be unlikely to pursue adjuvant chemotherapy for her lung cancer – as was indeed the situation here.

References:
been unimpressed with local control rates using WBRT. When a patient such as this one develops distant metastasis, I refer the patient for Cyberknife treatment. Dr Linson may have more to add on this possibility.

**Dr Linson [UCSD]:** Whole-brain radiotherapy (WBRT) is unjustifiably viewed as totally ineffective in cases of brain metastases. The reality is that for a patient with multiple metastases and a poor prognosis, WBRT is the only thing we can do. With a solitary brain metastasis, as in this case, resection provides the highest likelihood of survival. There are no prospective, randomized trials comparing surgery to radiosurgery, but outcomes are fairly equal in cases such as this. For patients who refuse surgery or who aren’t good candidates for surgery due to multiple medical co-morbidities or other reasons, radiosurgery is an option. Fortunately, with single-fraction radiosurgery, using either a Gamma-Knife or Cyberknife, local control rates are approximately 90% to 95%, with limited morbidity. With radiosurgery for a 4 mm enhancing lesion, such as in this case, there is quite a good likelihood of control with limited morbidity. Melanoma patients do as well with this treatment as patients with primary lung or breast tumors.

**Dr Easter [UCSD]:** This patient is going to have more metastatic disease, most likely from the primary melanoma.

**Dr Mastrangelo [TJU]:** For the lesion found on the cortical surface of the operculum, I would recommend intense local radiation, whether IMRT or Gamma-Knife.

**Dr Wolchok [MSK]:** Regarding treatment of the metastases itself, I don’t think it matters whether the metastases are from the lung cancer or from the melanoma. For the small, solitary brain metastasis, focused, high-dose RT, either Gamma-Knife or stereotactic radiosurgery, would be the treatment of choice.

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**Brain Metastases**

Brain metastases are a frequent development in advanced melanoma, and sometimes are the initial site of metastatic disease. Gadolinium-enhanced MRI scans of the brain are very sensitive for detecting small metastases, and the widespread use of these scans has increased the frequency with which we encounter small, solitary brain metastases in clinical practice. This earlier detection has led to longer survival times from initial diagnosis of brain metastasis, but whether this represents a true alteration of the natural history or mere “lead time bias” is not always clear. Nonetheless, faced with this new finding, aggressive treatment is indicated – and this time it makes little difference whether the culprit is the melanoma or the lung cancer. Both would best be treated with stereotactic radiation of one form or another: stereotactic surgery, Gamma Knife and Cyber-knife being just some of the terms used for intense, focused radiation delivered very precisely in one or a few sessions. Stereotactic radiosurgery (SRS) has generally been limited to patients with 1-3 metastases, but increasingly experienced centers are treating selected patients with larger numbers of lesions.1,2

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**Figure 3-8.** CT/PET fusion showing multiple liver metastases as well as hypermetabolic retroperitoneal and mediastinal nodes.

Source: Photomicrographs provided by Jane Messina, MD
Even when radiation results in control of the disease in the central nervous system, extracranial progression of melanoma is commonplace. Because of this, there has been considerable interest in combining stereotactic and/or whole brain radiation with systemic chemotherapy, particularly with temozolomide – which crosses the blood-brain barrier. Although this strategy has theoretical and practical appeal, clinical trial data supporting its use is lacking.

**Dr Zager:** The patient did receive stereotactic RT to the brain and did very well. Four months later, MRI of the brain revealed complete resolution of the operculum lesion with no new disease. However, LDH was markedly elevated at 1.8 times the upper limit of normal. A new PET-CT scan (Figure 3-8) showed multiple liver metastases and hypermetabolic retroperitoneal lymph nodes.

**Q** What further evaluation and/or treatment do you now recommend, and does it matter if these metastases are from the lung tumor or from the melanoma?

**Dr McClay [UCSD]:** From my perspective, it does matter whether these are lung or melanoma metastases. I would perform an FNA biopsy of the site that the interventional radiologists believed to be most accessible, and then tailor the therapy based upon whether the new lesions are caused by the lung cancer or the melanoma. There is a difference, and I would want to know whether the metastases are from the lung cancer or melanoma before choosing a systemic therapy.

**Dr Linson [UCSD]:** If this were an isolated lesion in the liver or a limited number of metastases, and the interval between resection of the primary tumor was reasonably long, one could argue that reducing tumor burden in this patient by Cyberknife radiosurgery could be helpful. The schedule would be three or four fractions over 1 week. If the RT is delivered away from the porta hepatis and that portion of the liver adjacent to the stomach, where ulceration with higher doses of radiosurgery can occur, morbidity would likely be limited. If the patient had widespread, multiple lesions, neither conventional RT nor radio-surgery would be likely to help.

**Dr Easter [UCSD]:** Systemic lesions require systemic therapy. For one or two isolated lesions in the liver, we might offer ablative, not resectional, therapy. Percutaneous radiofrequency ablation of isolated liver lesions, which can be laparoscopically directed, would be a rational approach for this patient.

**Dr Mastrangelo [TJU]:** When considering systemic treatment, it makes some difference whether she has lung cancer or melanoma metastatic to the lung and liver. A liver biopsy would be necessary to determine this. In either case, the treatment is going to be toxic and the outcome is not likely to be favorable. I would discuss systemic treatment with this patient, clearly communicating its cost/benefit ratio.

**Dr Wolchok [MSK]:** If PET/CT scanning found multiple hepatic metastases and hypermetabolic retroperitoneal lymph nodes, their origin does matter, because treatment then would be different. A fine-needle biopsy of the liver would be indicated.

Most clinical studies would exclude this patient, based upon either the brain metastasis or the second malignancy found within a short period. The standard treatment modalities for this patient after metastatic melanoma is confirmed would be either dacarbazine or high-dose IL-2. However, neither would be likely to help significantly. Combination chemotherapy, such as the Dartmouth regimen (dacarbazine/cisplatin/carmustine/tamoxifen) or CVT (cisplatin/vinblastine/temozolomide) would be a reasonable alternative to offer this patient.

**Nurse Roman [MSK]:** This patient may be eligible for a randomized clinical trial of a vascular endothelial growth factor (VEGF) inhibitor plus or minus dacarbazine, which is now being conducted at MSKCC.

**Dr Wolchok [MSK]:** Knowing the toxicities of IL-2, especially in elderly patients, it makes sense to offer a novel therapy to elderly patients with metastatic disease, such as this one.

### References

### Evaluation and Treatment Considerations
The patient now has clear evidence of widespread metastatic disease, but it is not possible to determine radiologically whether these metastases arose from the patient’s melanoma or her lung cancer. This is a clinically important distinction, because the systemic therapy options are so different. Although, if absolutely needed, a treatment plan could plan be formulated without knowing the diagnosis, guided biopsy of one of the metastases is feasible and should be per-
treatment regimen? As pointed out by the discussants, a patient like this with two primary malignancies as well as re-treated brain metastasis is unlikely to qualify for a clinical which is often the first-line “treatment of choice” for mel- ama. High-dose interleukin-2 is an appropriate consideration in the older patient, but this patient’s age argues strongly against this approach. Other immunologic approaches would normally be considered, but most of the promising emerging therapies (such as BRAF inhibitors or anti-CTLA-4 antibodies) are currently available only to patients on clinical trials. Most likely, this pa-tient would be treated with systemic chemotherapy. Single-agent dacarbazine (DTIC) or the related oral agent temozolomide are viable first-line approaches, albeit with low response rates in patients with M1C disease such as this. Of the two drugs, we would prefer temozolomide, because it crosses the blood-brain barrier, for this patient who has already been treated for one brain metastasis. Combination chemotherapy would also be an option, one that has never been conclusively proven to improve survival compared to single agent therapy. Generally, a platinum compound is combined with DTIC or paclitaxel; the combination of carboplatin and paclitaxel is an increasingly widely used standard regimen (and, since it has activity against lung cancer, would be the regimen of choice if a definitive diagnosis of the nature of the metastases could not be established).1-5

References

The three cases included in this monograph cover a broad range of commonplace (and some rare) clinical scenarios in the management of primary and metastatic melanoma. Reviewing the discussion and comparing the management strategies of the various melanoma centers indicates the lack of uniformity in approach to such fundamental aspects as surgery, staging and follow-up, adjuvant therapy and systemic therapy. There are few if any “right answers” to the questions posed about the management of these cases, and virtually all the participants referred repeatedly to the desirability of enrolling patients onto clinical trials whenever feasible. Only through carefully designed and conducted clinical trials will some of the most vexing questions facing us and our patients be answered.

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Closing Comments
1. Surgery may be considered as a treatment option for patients with melanoma that is
   a. Stage IIB
   b. Stage III
   c. Stage IV
   d. Any stage

2. Regional nodal recurrence of melanoma has been correlated with
   a. Ulceration of the primary tumor
   b. Whether the primary arose from the pre-existing nevus
   c. Diameter of primary lesion
   d. All of the above

3. An agent indicated for the treatment of metastatic melanoma in the US is
   a. Interleukin-2
   b. Sargramostim
   c. Interferon-α
   d. Trastuzumab

4. Survival of patients who undergo curative resection for distant metastases has been associated with
   a. Good performance status
   b. Extended disease-free interval before development of distant metastases
   c. Less aggressive tumor biology
   d. All of the above

5. Which factor has been shown to be the most powerful predictor for recurrence in clinically localized cutaneous melanoma?
   a. Presence or absence of ulceration of primary tumor
   b. Mitotic rate of the primary tumor
   c. Breslow depth of the primary tumor
   d. Sentinel lymph node status
   e. Presence or absence of regression in the primary tumor

6. A factor that is independently predictive of survival in melanoma patients with pulmonary metastases is
   a. Metastectomy
   b. Percent of tumor shrinkage post-RT
   c. Response to INF-alpha
   d. All of the above

7. The lung is the most common site of metastasis in patients with melanoma
   a. True
   b. False

8. Which of the following primary tumor factors portends an increased risk of a positive sentinel node biopsy for melanoma?
   a. Ulceration of the primary tumor
   b. Nodular melanoma subtype
   c. Location on the head and neck regardless of Breslow depth
   d. Breslow depth less than 1.0 mm
   e. Clark’s level III invasion
9. Treatment of brain metastasis may include?
   a. Surgery
   b. Whole brain radiation therapy
   c. Stereotactic radiosurgery
   d. All of the above

10. Autopsy studies indicate that more than half of patients who die of melanoma have metastases of the CNS
   a. True
   b. False

TIME SPENT ON THIS ACTIVITY: HOURS _____ MINUTES _____
(READING ARTICLES AND COMPLETING THE LEARNING ASSESSMENT AND EVALUATION)


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EVALUATION (must be completed for your CME Quiz to be scored)
Using the scale below, circle the number that corresponds with your opinion for each item.

1 = poor; 2 = fair; 3 = satisfactory; 4 = good; 5 = excellent

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4. Please rate the degree to which the content presented in the activity was free from commercial bias.
   No bias 4 3 2 1
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5. List one new thing you learned that can be applied to your practice:
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