MELANOMA CARE OPTIONS™

MARCH 2009

FOSTERING AN INTERDISCIPLINARY APPROACH TO MELANOMA CARE

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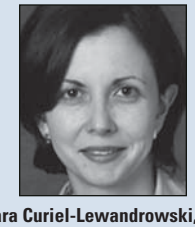


Clara Curiel-Lewandrowski, MD

Issue 2: Advances in Melanoma Staging and Surgical Techniques

Editor's Note...

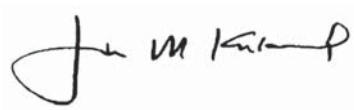
Dear Colleague,

Welcome to the second issue of the latest Melanoma Care Options publication series from the Melanoma Care Coalition, designed to provide you with expert interpretation on areas of evolving knowledge and controversy in melanoma management. This issue focuses on decisions that confront clinicians when evaluating and treating primary melanoma. For patients with early melanoma, prognosis is heavily dependent on features associated with primary and regional disease. Accordingly, information derived from careful work-up and staging procedures are critical to appropriate disease management.

The 3 cases presented here involve the staging of melanoma according to the new 7th Edition American Joint Committee on Cancer staging system for cutaneous melanoma, biopsy of primary melanoma and treatment of melanoma in situ, and the use and interpretation of sentinel lymph node biopsy. Each case is accompanied by faculty recommendations and a review of relevant data. The opinions herein are those of the authors. They are based on currently available data and clinical experience, and may change as new findings emerge.

As editor of this issue of Melanoma Care Options, I would like to thank you for participating in this interdisciplinary dialogue. As always, we welcome your remarks on the series and encourage you to participate in other Melanoma Care Coalition programs—see www.MelanomaCare.org for other offerings, all of which promise to improve our ability to care for patients.

Sincerely,



John M. Kirkwood, MD

Additional melanoma information now available at www.MelanomaCare.org or www.MelanomaNurse.org

Clinical Perspectives in Melanoma
A Report on Advances in Melanoma from the 2008 European Society for Medical Oncology (ESMO) Meeting, Stockholm, Sweden, September 12-16, 2008

Insights in Melanoma
Highlights from the Perspectives in Melanoma XII Meeting, The Hague, The Netherlands, October 2-4, 2008

Continuing Medical Education Information

Instructions for Participation:
- Read the case presentations and comments in the publication
- Complete the posttest questions and evaluation form at the end of the newsletter and fax or mail them to the UPMC Center for Continuing Education

To receive a maximum of 1.5 *AMA PRA Category 1 Credits*™ for this activity:
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Target Audience
This activity is directed toward surgical oncologists, oncology nurses, medical oncologists, dermatologists, and other health care professionals who treat or screen for melanoma.

Statement of Need
Management of all stages of melanoma requires a concerted effort on the part of several specially trained members of a healthcare team. Assessing risk, getting patients into the healthcare system, evaluating prognostic information, analyzing and interpreting new therapeutic information and choosing appropriate therapy, working as a team, and educating, guiding, and motivating the patient remain challenging. A core group of specialists are knowledgeable about the optimal management of this malignancy, and this activity provides their insight for practicing healthcare providers.

Learning Objectives
After completing this activity, participants should be able to:
- Interpret changes to the latest edition of the AJCC staging system for cutaneous melanoma and extrapolate those changes to clinical practice
- Describe different biopsy techniques and identify clinical situations best-suited for each procedure
- Evaluate techniques employed in Mohs micrographic surgery and staged excision
- Appraise the value of imiquimod as treatment for melanoma in situ
- Analyze controversies regarding the use of sentinel lymph node biopsy and the interpretation of biopsy findings

Accreditation and Credit Designation
The University of Pittsburgh School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The University of Pittsburgh School of Medicine designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Each physician should claim only those credits commensurate with the extent of his or her participation in the activity.

1.5 contact hours of Continuing Nursing Education will be granted by the University of Pittsburgh Medical Center. The University of Pittsburgh Medical Center is an approved provider of continuing nursing education by the Pennsylvania State Nurses Association (PSNA), an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

We gratefully acknowledge an educational grant from Schering-Plough Corporation in support of this activity.

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Staging Melanoma: Preview of Changes in the 7th Edition of the AJCC Staging Manual

By John M. Kirkwood, MD, and Robert H. I. Andtbacka, MD, CM, FRCS(c)

CASE PRESENTATION

A 36-year-old man presents with a shaped, pigmented, nonulcerated skin lesion on his upper chest that measures 1.5 cm wide. Biopsy confirms malignant melanoma. The tumor has a thickness of 0.8 mm, a Clark invasion level of II, and a mitotic rate of 3/mm^2. How would you stage this patient?

1. Clinical/pathologic at least stage IA with a T1a tumor
2. Clinical/pathologic at least stage IB with a T1b tumor

Stage IA is correct as per the 6th Edition of the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma.[1] However, in the 7th Edition of the staging system (expected in 2009), stage IB is correct. Although the 7th Edition does not herald a dramatic departure from staging criteria used in the 6th Edition, there are some important differences (**Table 1**). The following sections will provide a preview of the new AJCC recommendations along with explanations of the rationale behind the changes.

Challenges for Staging

The appropriate staging of patients with cancer is critical to patient management. Accurate staging of cancer supplies important prognostic information and allows rational treatment recommendations. It is also important in providing trial stratification criteria, which facilitate comparisons of uniform populations in clinical trials.

The ideal cancer staging system should be simple and universally applicable. It should be based on prognostic and predictive factors that enable us to predict patient outcome in terms of relapse and mortality as well as guiding patient and physician with regard to options in therapy. Although melanoma staging has not yet reached this ideal, it has come a long way in identifying homogeneous groups based on patient and disease characteristics. Through an evidence-based approach made possible by an international database of melanoma patients from large institutions and cooperative groups, melanoma staging criteria have begun to incorporate increasingly discriminating prognostic factors. This evolving process is ongoing, and at the moment is between 6th and 7th Editions for the AJCC Melanoma Subcommittee.

The 6th Edition of the AJCC staging system emphasized Breslow thickness, ulceration, the number of metastatic lymph nodes, and the site of distant metastases as key prognostic criteria. The resulting classification system defined melanoma stages that clearly predicted survival.[1] Nevertheless, this system had important limitations. Some major stage categories showed significant prognostic heterogeneity, resulting in prognostic overlap between some substages. For instance, patients with pathologic stage IIC melanoma have a 5-year survival rate of 45% compared to 70% for stage IIIA melanoma that would, on the surface of the nomenclature, seem to be a more advanced disease stage.[1]

With the 7th Edition, the AJCC maintained the fundamental UICC tumor-node-metastasis (TNM) classification system, utilizing multivariate analyses of the international database to identify additional prognostic markers. The goal was to establish stage groupings that minimized prognostic heterogeneity and overlap. The Committee analyzed an international database of 60,000 patients from 14 cancer centers and organizations. Data from this large cohort of patients allowed the analysis and validation of multiple prognostic factors and staging categories (CM Balch, personal communication).

Updates to Tumor Classification

One of the most important changes in the AJCC 7th Edition relates to the criteria used to define thin (T1) melanomas (≤1.0 mm), the most frequent presenting category of melanoma.[1] In the 6th Edition, T1a and T1b melanomas were distinguished by the presence or absence of ulceration and/or by the Clark level of invasion.[1] Analyses of prognostic factors conducted at that time found that although level of invasion was a significant prognostic variable in univariate analyses, the significance of this variable was not retained in multivariate analyses.[2] Subsequent studies have confirmed that Clark level

Table 1. Potential Benefits and Risks Associated With Receipt of Positive or Negative Test Results for Mutations in Melanoma Susceptibility Genes

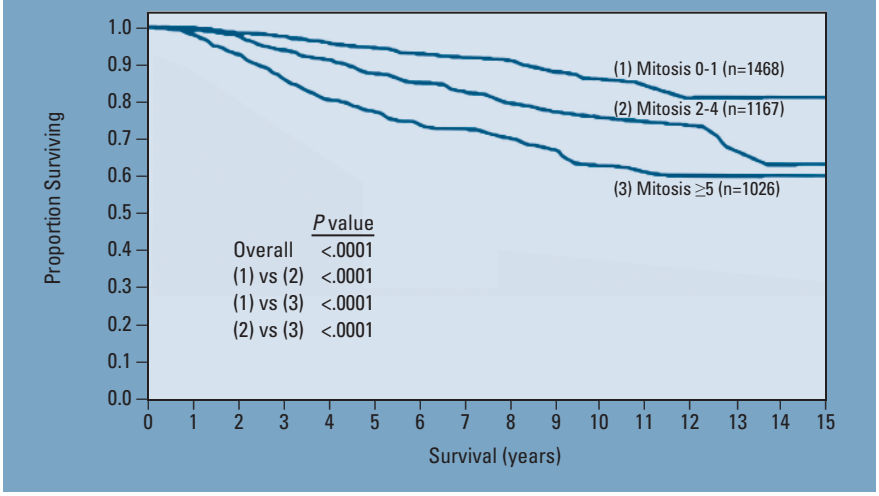
Category	6th Edition AJCC[a]	7th Edition AJCC[b]
T1 staging (≤ 1.0 mm)	a. without ulceration and Clark level II/III b. with ulceration or Clark level IV/V	a. without ulceration and mitoses <1/mm^2 b. with ulceration or mitoses ≥ 1/mm^2
Nodal metastases	Detection by H&E staining only	Detection by H&E OR IHC staining with at least 1 melanoma-specific marker (eg, HMB-45, Melan-A/MART-1); no lower limit in the size of metastases when staging node-positive melanoma
Staging of metastatic melanoma from an unknown primary site	Not specifically addressed	Metastases in lymph nodes, skin, and subcutaneous tissues should be categorized as stage III. Metastases in other locations should be categorized as stage IV

H&E, hematoxylin and eosin; IHC, immunohistochemical.
[a] Balch CM et al. *J Clin Oncol.* 2001;19(16):3635-3648.[1]
[b] Balch CM, personal communication.

of invasion is not a significant prognostic indicator in multivariate analyses, especially when mitotic rate of the primary tumor was considered. By contrast, mitotic rate has emerged as a highly significant prognostic variable.[3,4] In a multifactorial Cox regression analysis of more than 10,000 melanoma patients with localized melanoma, mitotic rate proved to be second after tumor thickness as a predictor of survival (CM Balch, personal communication). On the basis of these data, mitotic rate has been introduced as a new required element for the staging of primary tumors in the AJCC 7th Edition.

The AJCC recommends that the mitotic rate of primary tumors be measured as the average number of mitoses per square millimeter. If possible, mitoses should be counted in the area containing the most frequent mitotic figures. The best survival rates were found with 0 or 1 mitoses/mm^2 (**Figure 1**).[4] If mitotic rate cannot be accurately determined, it is still acceptable to use Clark invasion level IV or V to categorize tumors as T1b (CM Balch, personal communication).

Figure 1. Impact of Increasing Mitotic Rate (mitoses/mm^2) on Survival in 3,661 Patients With Localized, Cutaneous Melanoma



From Azzola AF et al. *Cancer.* 2003;97(6):1488-1498.[4] Copyright © 2003 American Cancer Society. Reproduced with permission of John Wiley & Sons, Inc.

Case Continued

The patient is staged as T1b in keeping with the upcoming AJCC 7th Edition. Further examination fails to detect palpable lymph node masses. Would you encourage the patient to undergo lymphatic mapping and sentinel lymph node biopsy (SLNB)?

1. Yes, this procedure may provide important prognostic information.
2. No, the risk of nodal involvement is too low to recommend SLNB for this patient.

The faculty recommends that SLNB be performed (choice #1), as this procedure provides critical prognostic information and may help guide treatment decisions. Analyses of the 2008 AJCC melanoma database have confirmed the significance of SLN status as the most important factor in determining prognosis (**Figure 2**). Both the 7th Edition AJCC staging system (CM Balch, personal communication) and The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Melanoma[5] recommend that SLNB be encouraged for patients with stage IB melanoma.

The faculty acknowledges, however, that SLNB in patients with thin (≤1 mm) melanomas remains a controversial topic. Approximately 1.1% to 13.5% of patients with thin melanomas have nodal metastases, and experts are divided as to whether SLNB is indicated in this patient population.[6-8] Most patients with thin melanomas and nodal metastases have melanomas between 0.75 and 1 mm in thickness; nodal metastases are extremely uncommon in patients with melanomas <0.75 mm.[6-8] Other risk factors for nodal involvement in patients with thin melanomas include mitotic rate, Clark level of invasion, and younger patient age.[6,9]

Despite the low level of nodal metastases in patients with thin melanomas, an analysis of 631 patients with thin melanomas who underwent SLNB found that positive SLN remained a significant prognostic feature. The 10-year disease-free survival rates were 96% in SLN-negative patients compared with 54% in SLN-positive patients.[9] Because of the important prognostic information provided by SLNB and the fact that the case study patient has 3 risk factors for nodal involvement (thickness >0.75 mm, elevated mitotic rate, and young age), the faculty concludes that this patient is an appropriate candidate for SLNB.

Case Continued

The patient undergoes lymphatic mapping and SLNB. No micrometastases are detected with hematoxylin and eosin (H&E) staining, but immunohistochemical (IHC) staining with MART-1 and S-100 identifies 1 involved axillary node with a single micrometastasis of 0.16 mm in diameter. Should this patient be considered node positive?

1. Yes
2. No

The faculty recommends that this patient be considered node positive (choice #1), which changes his clinical stage to stage III (regional disease) and his pathologic stage to stage IIIA (nonulcerated primary tumor and micrometastasis in 1 node). As discussed in the subsequent section, the AJCC 7th Edition expands on the role of IHC staining in histopathological analyses of lymph nodes and clarifies the absence of a lower threshold for staging a patient with SLN-positive disease. That is, the observation of any tumor cell in a lymph node containing microscopic tumor suffices to designate the patient as stage IIIA.

Changes in Nodal Staging

Changes to nodal staging in the AJCC 7th Edition mainly focus on methods that may allow improved detection of positive lymph nodes and clarification of what constitutes a positive lymph node. The major prognostic criteria identified for SLN-positive patients in the AJCC 6th Edition (number of metastatic lymph nodes, tumor burden, ulceration of the primary tumor, and the presence of satellite or in-transit metastases)[1] remain key prognostic factors in the AJCC 7th Edition.

IHC staining for melanoma-associated markers is now widely available and can improve the diagnostic sensitivity of SLNB, particularly when combined with conventional H&E staining.[10] The AJCC Melanoma Subcommittee has therefore changed the 6th Edition standard, which mandated H&E staining in the assessment of nodal pathology,[1] to allow IHC staining for histopathologic confirmation of nodal metastases. At least 1 melanoma-associated marker (eg, HMB-45, Melan-A/Mart 1) must be used if cellular morphology is not otherwise diagnostic. Furthermore, the Subcommittee recommends that IHC staining be performed in conjunction with H&E staining to improve diagnostic sensitivity (CM Balch, personal communication). The use of IHC is supported by data from the Sunbelt Melanoma Trial, a multicenter, prospective, randomized study of patients with clinically negative regional lymph nodes. In this trial, patients with SLN metastases detected only by IHC staining had similar rates of non-sentinel node involvement as patients with SLN metastases detected by H&E staining, providing confirmation of the clinical relevance of micrometastases detected by IHC.[11]

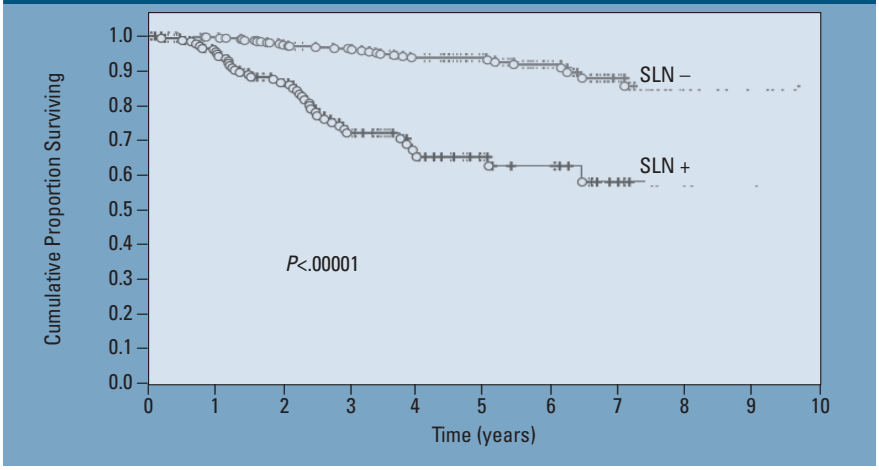
Most laboratories use 2 or more markers for IHC staining. Current data suggest that S-100 is the most sensitive marker (97% to 100%), but its specificity is only about 80%. In contrast, HMB-45, MART-1/Melan-A, tyrosinase, and MITF have greater specificity, but are not as sensitive. In addition, spindle cell and desmoplastic melanoma lesions do not generally stain with these more specific markers.[12]

Improved detection methods have raised the question of whether there is a threshold below which micrometastases should be considered "not clinically relevant." For breast cancer, isolated tumor cells (ITC) or cell clusters ≤0.2 mm are staged as node negative, as per the 6th Edition of the AJCC cancer staging manual, and do not appear to have a negative impact on prognosis.[13,14] For melanoma, however, the AJCC Melanoma Staging Subcommittee concluded that a safe threshold of tumor burden cannot be defined at this time. Accordingly, there is no lower threshold for staging a patient with node-positive melanoma by conventional H&E or IHC staining techniques (CM Balch, personal communication).

Nevertheless, the existence of a lower threshold for SLN-positive status remains a controversial issue in melanoma, particularly for very small metastatic deposits. One key study that supports the AJCC recommendation assessed the occurrence of ITC (defined as ≤0.2 mm) in the SLN of patients with stage I/II melanoma.[15] A total of 214 of 1,382 patients had tumor-positive SLN, and approximately one-fourth of the SLN-positive patients (57 of 214; 26.6%) had metastases limited to ITC. CLND identified non-SLN metastases in 6 of 52 patients (12%) with ITC. Furthermore, patients with ITC had a significantly higher risk of melanoma-specific death than patients with tumor-negative SLN, indicating that micrometastases ≤0.2 mm have clear clinical significance.

In contrast to these findings, a smaller study involving 74 patients reported that micrometastases <0.1 mm were not associated with non-SLN metastases and did not affect overall survival. These authors concluded that such micrometastases can be safely staged as node negative.[16] There is also evidence that metastatic disease identified by molecular means only does not have prognostic significance. In a study in which reverse transcriptase-polymerase chain reaction (RT-PCR) technology was used to detect melanoma-specific mRNAs in histologically-negative SLN tissue, no difference was observed in overall survival, disease-free survival, or distant disease-free

Figure 2. Disease-Specific Survival by SLN Status in the 2008 AJCC Melanoma Database



From Ross MI. New AJCC Recommendations for Melanoma Staging. Presented at: 33rd ESMO Congress Satellite Symposium: *Current Trends in Melanoma Management*; September 14, 2008; Stockholm, Sweden.

survival in patients with RT-PCR-positive SLN compared to those with RT-PCR-negative SLN.[17] Because RT-PCR-based staging lacks standardized techniques or markers and its prognostic significance is unclear, these methods are not recommended for use in melanoma staging at this time (CM Balch, personal communication).

Staging of Melanoma from an Unknown Primary Site

Staging of melanoma from an unknown primary site can pose significant clinical challenges. This topic was not specifically addressed in the AJCC 6th Edition. The 7th Edition clarifies that patients with isolated metastases arising in the lymph nodes, skin, and subcutaneous tissues, and with no other sites of metastases detected during a thorough staging workup, should be considered to have regional (stage III) rather than metastatic disease (stage IV) (CM Balch, personal communication). This decision was based on studies demonstrating that patients with regional lymph node metastases from an unknown primary site had survival rates comparable to or more favorable than patients with nodal disease and a known primary.[18,19] The most recent study involved analyses of outcomes from a database of over 13,000 melanoma patients who had undergone regional lymphadenectomy.[19] Survival rates for 262 patients with melanoma from an unknown primary site were compared to survival rates from 1,309 matched patients. The 5-year median and overall survival rates were significantly higher for patients with an unknown primary (165 months and 58%, respectively) than for patients with a known primary (34 months and 40%, respectively; P=.0006).[19]

The more favorable prognosis associated with an unknown primary suggests that an endogenous immune response against the primary melanoma may improve outcomes, and that melanoma from an unknown primary should be treated aggressively with a curative intent.[18,19] It is thus more appropriate to stage patients with an unknown primary and localized metastases to the lymph nodes, skin, or subcutaneous tissues as stage III than as stage IV. For all other circumstances, such as metastases to a visceral site and unknown primary, patients should be classified as stage IV (CM Balch, personal communication).

Conclusion

The new staging criteria recommended by the AJCC Melanoma Staging Subcommittee reflect evolving technology, which allows new methods of evaluating metastatic disease, as well as new insights derived from analyses of the international database. Refinement of prognostic groups is essential to assessing metastatic risk and predicting relapse and survival. Such knowledge allows clinicians and their patients to balance the benefit to risk ratio of various treatment options. In addition, careful staging allows accurate stratification in clinical trials, thus providing data that can allow future AJCC Subcommittees to further refine and differentiate key prognostic criteria in patients with melanoma.

New Insights Into the Surgical Management of Pigmented Lesions and Treatment of Melanoma In Situ: Biopsy, Mohs Micrographic Surgery, and Imiquimod

By Clara Curiel-Lewandrowski, MD

CASE PRESENTATION

A 62-year-old man presents for evaluation of a 12-mm pigmented, irregularly-shaped patch with poorly demarcated margins located on his nose. The "mole" had been present for approximately 10 years, but during the past 8 months the patient's wife noted that it had increased in size and pigmentation. His primary care physician recommends a biopsy. What type of biopsy would you perform?

1. Shave biopsy
2. Punch biopsy (8-mm)
3. Multiple incisional biopsies guided by dermoscopy
4. Saucerization
5. Narrow surgical excision (1- to 3-mm margin)
6. Wide local excision (5- to 8-mm margin)
7. 1, 2, and 6
8. 3 or 5

The faculty recommends multiple incisional biopsies or narrow surgical excision (choice #8). Given the location of the lesion and the risk of significant cosmetic disfigurement, multiple incisional biopsies is a reasonable option, even though the guidelines from the NCCN and the Guidelines/Outcomes Committee of the American Academy of Dermatology (AAD) state that excisional biopsy with narrow (1- to 3-mm) margins (choice #5) is the preferred method for investigating suspicious lesions.[5,20] Saucerization (choice #4) is not usually applied to lesions of this size on the face and close to the eye.

Methods of Biopsy for Pigmented Lesions

The appearance of a suspicious pigmented lesion is a common reason for visits with numerous categories of clinicians who are responsible for biopsy decisions. In general, the most accurate evaluations of suspicious lesions are obtained at pigmented skin clinics, followed by dermatologists.[21] In some cases, the patient may request a biopsy due to specific concerns or to enhance their peace of mind.

Biopsies can be classified as "incisional" (partial removal of the lesion) or "excisional" (complete removal of the lesion). Incisional biopsies are appropriate when the suspicion of melanoma is low or when the lesion is large or in a location that does not allow for complete excision.[20] There are several types of biopsy, including shave biopsy, saucerization, punch biopsy, and surgical excision. Some techniques, such as punch and shave biopsy, are incisional biopsies when applied to a large lesion but act as excisional biopsies if used on a small lesion.

Shave biopsies are the most common technique because they are quick, inexpensive, and have excellent cosmetic results. However, shave biopsies are generally superficial and may not include deeper tissues. Accordingly, this form of biopsy should not be used if invasive melanoma is suspected. Saucerization involves a deep shave or scoop technique and usually extends into the deep dermis or superficial subcutaneous layer. If the lesion is small and shallow, saucerization may be able to remove the complete lesion. If deeper tissue involvement is suspected, a punch biopsy is a possible alternative. This technique removes a cylindrical core of tissue containing samples of the epidermis, dermis, and occasionally subcutaneous fat. Surgical excision involves the use of a scalpel to completely remove the suspect lesion.[21,22] Narrow (1- to 3-mm) margins are recommended. Wider margins are discouraged, as they may interfere with subsequent lymphatic mapping. The AAD further recommends that fine needle aspiration not be used to evaluate the lesion, and both the NCCN and AAD recommend that all biopsies be evaluated by a pathologist experienced in pigmented lesions.[5,20]

For incisional biopsies, appropriate sampling is an important issue, since the diagnosis is dependent on the exact portion of the nevus examined (**Figure 3**). The NCCN recommends that the clinically thickest portion of the lesion be examined if an incisional biopsy technique is used.[5] Incisional biopsies run the risk of sampling nonmalignant areas of tissue, resulting in misdiagnosis. Although the AAD concluded that an incisional biopsy does not adversely affect patient outcome,[20] a study in patients with cutaneous head and neck melanoma found significantly increased mortality rates in patients receiving incisional biopsies compared with those who received excisional biopsies (31.3% vs 8.9%, respectively).[23]

Case Continued

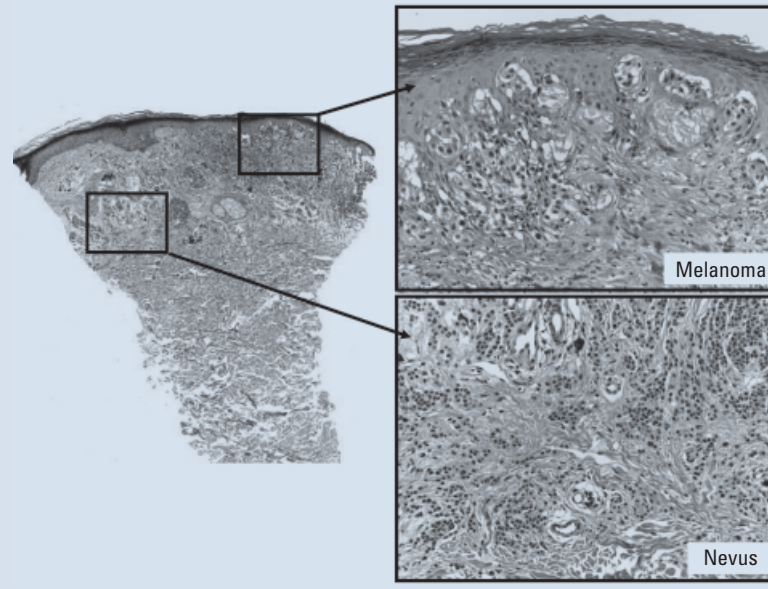
Despite his physician's recommendation of an excisional biopsy of multiple incisional biopsies, the patient opts for a single punch biopsy due to cosmetic concerns. Histopathologic examination of the tissue indicates the presence of melanoma in situ, lentigo maligna type (**Figure 4**). The patient remains concerned about cosmesis and the location of the lesion. Which of the following treatment options would you recommend?

1. Wide local excision with 5-mm margins
2. Wide local excision with 10-mm margins
3. Mohs micrographic surgery

The faculty recommends a wide local excision with margins as close to 5 mm as possible given the anatomic location (choice #1), although this may not be conducive to cosmesis. In the setting of melanoma in situ/lentigo maligna, Mohs micrographic surgery could be considered a therapeutic option if performed by an experienced surgeon. Regardless of the method used, careful margin assessment is essential, as many head and neck melanomas require more extensive margins than the 5-mm (0.5-cm) margin recommended by the NCCN and the AAD for melanoma in situ.[5,20] Zalla and colleagues found that an average margin of 8.3 mm was required for clearance in patients with melanoma in situ primarily located on the head and neck, and that margins of ≤6 mm resulted in clearance in only 50% of cases.[24] Other studies have reached similar conclusions,[25] including an analysis of 92 patients with lentigo maligna in which 5-mm margins were adequate in fewer than 50% of cases.[26]

In addition to close examination of peripheral margins, the margins of subcutaneous tissue should also undergo thorough histopathologic evaluation for evidence of invasive melanoma. An average of 23% (range, 5% to 67%) of lesions initially diagnosed as melanoma in situ have subsequently been found to have an invasive component.[25]

Figure 3. Uneven Distribution of Melanoma Within a Nevus



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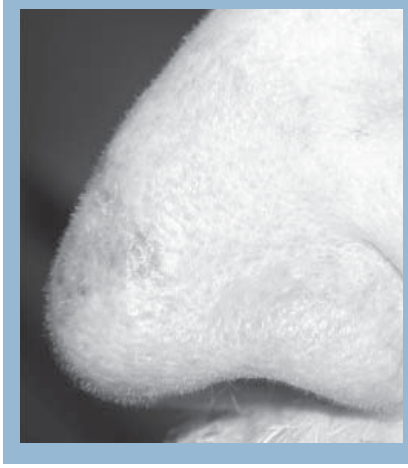
Mohs Micrographic Surgery in the Treatment of Melanoma In Situ

Melanoma in situ refers to melanoma cells that are confined to the epidermis and do not yet have an invasive component. Both clinically and pathologically, melanoma in situ is classified as stage 0.[1] This form of melanoma has an approximately 100% 10-year survival rate if managed appropriately.[27] The American Cancer Society estimates that 54,020 cases of melanoma in situ will be newly diagnosed in 2008.[28] Approximately 80% of melanoma in situ cases are of the lentigo maligna subtype, and the remaining 20% are superficial spreading melanoma.[29] Melanoma in situ lesions are believed to have the potential to progress to invasive melanoma, but the rate at which this occurs and the events that mediate this progression are unknown. For lentigo maligna, the risk of progression to lentigo maligna melanoma has been estimated to be as high as 50% and as low as 5%.[30]

Mohs micrographic surgery has some advantages in the treatment of melanoma in situ, including careful assessment of margins, tissue conservation, and excellent cure rates. Because of its intraoperative assessment of tumor margins, Mohs surgery is particularly well-suited to ill-defined lesions. Standard excisional surgery for melanoma in situ is associated with recurrence rates ranging from 6% to 20% with a follow-up of 3 years or more, and recurrence rates for patients undergoing Mohs surgery ranging

Figure 4. Melanoma In Situ, Lentigo Maligna Type



from 0% to 3.6% with a minimum follow-up of 18 months.[25]

The basic Mohs technique involves excision of the visible tumor and an additional layer of tissue surrounding the tumor, which is removed en face (parallel to the surgical margin). The orientation of the excised tissue is recorded by the use of a map and carefully placed reference marks. The tissue layer is frozen and assessed intraoperatively by histopathologic examination to determine whether all margins are free of tumor. If not, another Mohs layer is excised in the area of involvement and the process is continued. When the margins are no longer positive for tumor, the defect is repaired.[30]

The original Mohs micrographic surgery used frozen sections to allow rapid assessment of tumor margins. The damage caused by freezing can make it difficult to accurately identify melanocytes present in frozen tissue sections and to differentiate between melanoma and benign melanocytic hyperplasia found in normal sun-damaged skin.[25,30] Although some clinicians have reported extremely high sensitivity and specificity in detecting melanoma in frozen sections compared with paraffin-embedded sections, others report less favorable results. For instance, Zitelli and colleagues analyzed 221 specimens and reported 100% sensitivity and 90% specificity in detecting melanoma.[31] In contrast, Barlow and associates determined a sensitivity of 59% and a specificity of 81% in their evaluation of 50 difficult-to-interpret specimens.[32]

The problems with frozen sections have led some clinicians to use permanent sections to assess margin control. Although sometimes referred to as Mohs surgery, these staged excision methods typically do not allow intraoperative margin assessments as with true Mohs micrographic surgery.[30] The key features of Mohs micrographic surgery and staged excision with permanent sections are shown in **Table 2**.[30,33]

A combination approach has been used by some clinicians. This modification employs conventional Mohs micrographic surgery with frozen sections until equivocal or clear margins are determined, and then uses permanent sections until clear margins are confirmed (**Table 2**). The advantage of same-day closure is lost, but accuracy may be improved.[30] A recent study of this approach in the treatment of melanoma in situ found that assessment of frozen sections alone missed 8 of 167 cases (95.1% clearance rate).[34] All 8 cases achieved clear margins following re-excision with 3-mm margins.[34]

Another modification to the original Mohs procedure is to employ melanocyte-specific IHC stains to improve the diagnostic accuracy of frozen sections. Staining takes about 90 minutes,[24] and thus this approach allows same-day margin assessment and wound closure.

Mohs micrographic surgery and related techniques thus have many advantages in the control of melanoma in situ, including the potential to improve cure rates and minimize defect size. These techniques are particularly well-suited to ill-defined lesions and those where cosmesis is important.[25] There are currently many variations of Mohs surgery, and research continues into ways to improve both speed and accuracy. Prospective, randomized trials are needed to further define the place of Mohs micrographic surgery in the treatment of melanoma in situ.

Case Continued

The patient undergoes 4 stages of Mohs micrographic surgery, but the margins remain positive. There is a significant risk of deformity with further surgery. What option would you recommend next?

1. Cryotherapy
2. Radiotherapy
3. Imiquimod
4. Laser therapy
5. 5-fluorouracil (5-FU)

The faculty recommends treatment with imiquimod (choice #3), an off-label use. As will be discussed in the following section, this topical therapy has resulted in favorable response rates in case series and small studies, although no randomized clinical trials have yet been conducted. Its ease of use and excellent cosmetic results make imiquimod an attractive choice. Other nonsurgical options for treating melanoma in situ include cryotherapy, laser therapy, radiotherapy, and 5-FU. Cryotherapy and laser therapy are both associated with high rates of recurrence when used to treat melanoma in situ (34.3% and 42.9% 5-year recurrence rates, respectively).[35] Retrospective studies suggest that radiotherapy is a viable option in the treatment of lentigo maligna and lentigo maligna melanoma and that recurrence rates are generally low (approximately 7% to 9%).[36,37] However, radiotherapy has some drawbacks, including the potential for radiodermatitis and skin cancer.[38] 5-FU, another topical therapy that has been used to treat lentigo maligna, is associated with high (up to 100%) recurrence rates and is not recommended as a therapeutic option for lentigo maligna.[39]

Imiquimod in the Treatment of Melanoma In Situ and Lentigo Maligna

The immunomodulating agent imiquimod has been approved by the US Food and Drug Administration (FDA) for the topical treatment of actinic keratosis, superficial basal cell carcinoma, and external genital and perianal warts.[40] This agent is a nucleoside analogue of the imidazoquinoline family and is administered as a 5% cream.[40,41] Imiquimod activates immune cells through interactions with toll-like receptors (TLRs) present on B cells; T cells; neutrophils; macrophages; and dendritic, endothelial, and epithelial cells, resulting in multiple biologic effects.[41,42] There is evidence that imiquimod operates through other pathways as well. For instance, it may have direct effects on B cell activities such as antibody production and proliferation. At elevated concentrations, imiquimod appears to exhibit pro-apoptotic activity against tumor cells.[41,42]

A number of small studies have evaluated the use of imiquimod in the treatment of cutaneous melanoma, particularly lentigo maligna. A recent analysis of studies with imiquimod conducted between 2000 and 2005 in patients with lentigo maligna identified 11 case reports and 4 open-label studies involving 67 patients.[43] Treatment regimens ranged from twice daily to once weekly, and the duration of treatment varied from 5 to 28 weeks. The combined response rate in these studies was 88%; 8 of the 67 patients (12%) did not respond to therapy. In several cases, there was a discrepancy between the clinical and the

Table 2. Methods of Peripheral Margin Assessment in the Treatment of Melanoma In Situ and Lentigo Maligna				
	MMS	MMS + Final Permanent Section	Staged Excision	
			Square	Radial
Angle of excision	45° or 90°	45°	90°	90°
Sectioning orientation	En face (horizontal or vertical)	En face (horizontal)	En face (horizontal)	Radial
Tissue fixation method	Frozen	Frozen followed by permanent	Permanent	Permanent
Reader of margin histologic findings	MMS surgeon	MMS surgeon and pathologist	Pathologist	Pathologist
Time to complete procedure*	Same day	Days	Days to weeks	Days

MMS, Mohs micrographic surgery.

*Typical time period for confirmation of disease-free margins for original procedures. More rapid modifications are being introduced.

Adapted from Bub JL et al. *Arch Dermatol.* 2004;140(5):552-558.[33] Copyright © 2004 American Medical Association. All rights reserved.
Additional data from Clark GS et al.[30]

histologic response, with some patients clearing clinically but not histologically, and vice versa. No relapses were detected in responding patients, but follow-up only extended to a maximum of 18 months.[43]

An open-label study published after this report evaluated imiquimod in the treatment of 34 lentigo maligna lesions.[44] Patients had not received previous treatment with other therapeutic modalities. Imiquimod was applied in various regimens, ranging from twice daily to 5 times per week, for a period of 2 to 20 weeks (median, 7 weeks). Patient follow-up at the time of the report ranged from 5 to 31 months. All 34 of the lesions completely cleared in response to imiquimod therapy. One lesion recurred after 30 months, but was successfully retreated with imiquimod. Other than transient irritation of the treatment area, no severe local or systemic reactions occurred, and none of the patients developed scars.[44]

Despite these excellent results, there are several potential drawbacks associated with imiquimod therapy. For patients treated with imiquimod, close, long-term clinical follow-up is essential. Discordance between clinical and histologic clearing in imiquimod-treated patients has been noted. In a study in which staged excision was performed following treatment of lentigo maligna with imiquimod (5 times per week for 3 months), 3 of 40 patients who appeared to have residual disease were found to be histologically clear, while 3 other patients judged to be clinically clear still had histologic evidence of residual disease.[45] Invasive disease has been observed in a small number of patients following imiquimod treatment,[45,46] including 1 case of amelanotic melanoma.[47] Recurrences, although rare, do occur.[44,48] A valid assessment of the frequency with which such negative events occur will require prospective clinical trials with long-term follow-up. Until such time as these data become available, clinicians should employ imiquimod with caution.

Conclusion

Pigmented lesions are a frequent cause of physician office visits. Excisional biopsy is the recommended method of evaluation of suspicious lesions. If an incisional biopsy is performed, adequate sampling should be ensured to allow an accurate diagnosis. Melanoma in situ is usually treated by excision to prevent progression to invasive melanoma. However, these lesions are often located on the head and neck and in other areas that complicate surgical removal. Mohs micrographic surgery offers a possible option for such lesions. The introduction of IHC and rapid staining techniques are likely to improve both the speed and accuracy of this technique. For in situ lesions for which surgery is not a viable option, topical imiquimod therapy has shown impressive results. Longer term data, preferably from controlled clinical trials, should provide further insights into the potential role of this immunomodulator in the treatment of melanoma in situ.

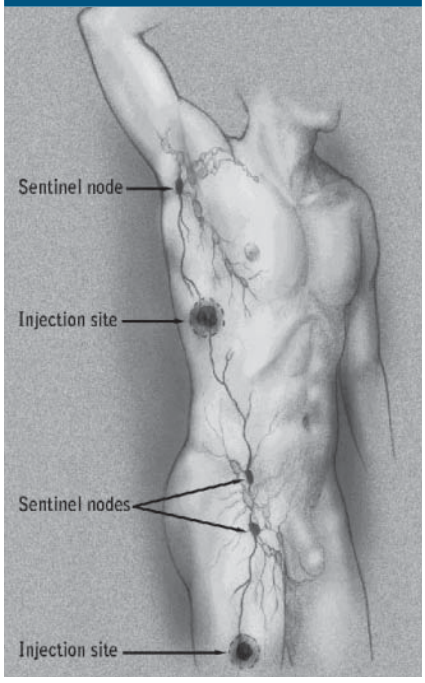
Sentinel Lymph Node Biopsy: Decoding the Controversies Surrounding its Use and Significance

By Robert H. I. Andtbacka, MD, CM, FRCS(c)

CASE PRESENTATION

A 30-year-old woman presents with a pigmented lesion 9 mm in diameter on her left thigh. The lesion has irregular borders, a raised darker central region with varying colors of black, dark brown, blue, and red. There is no palpable lymphadenopathy in the left groin, and the physical exam is otherwise unremarkable. A narrow margin excisional biopsy is performed of the thigh lesion and the pathology report indicates a superficial spreading cutaneous melanoma. The Breslow thickness is 1.8 mm, the Clark level is IV, and there is no ulceration. The lateral margins of resection are close but negative for melanoma. What would you recommend as the next step in the treatment of this patient?

Figure 5. Lymphatic Mapping



Blue dye identifies lymphatic drainage patterns from the area surrounding the tumor and allows visualization of the SLN.

Illustration courtesy of Jeffrey E. Gershenwald, MD.

1. No further treatment since the margins are negative for melanoma.
2. Wide local excision with a 2-cm margin.
3. Wide local excision with a 2-cm margin and a sentinel lymph node biopsy (SLNB).
4. Magnetic resonance imaging (MRI) of the brain and a computed tomography (CT) scan of the chest, abdomen, and pelvis.
5. An MRI of the brain and a whole body CT/positron emission tomography (PET) scan.

The faculty recommends a wide local excision with a 2-cm margin and a SLNB for this patient (choice #3). Although the surgical resection margins are clear, a wide local excision with a 2-cm margin is recommended to decrease the risk of local recurrence. This patient has a T2a tumor (Breslow thickness of 1.01 to 2.0 mm without ulceration) and her current clinical staging is stage IB.[1] NCCN guidelines recommend that SLNB be encouraged in patients with stage IB melanoma[5]. Routine staging imaging is not indicated in these patients before the regional lymph nodes have been assessed through SLNB.[5]

SLNB in Patients with Stage I/II Melanoma

In patients with early melanoma, nodal status is the most important prognostic factor.[1,49] This observation gave impetus to the use of lymphatic mapping and SLNB in the staging of patients with melanoma (**Figure 5**).

Approximately 15% of patients with stage I or II melanoma will have 1 or more positive SLN.[49-51] The risk is low (1.1% to 13.5%) in patients with thin (≤1 mm) melanomas, but increases significantly with increasing Breslow thickness.[6,7,49] A comprehensive review of SLN metastasis in thin melanoma will be published by Andtbacka and Gershenwald.[8] An analysis of 612 patients with stage I or II melanoma found that 4.8% of patients with primary melanomas ≤1.5 mm had a positive SLN; this proportion increased to 19.2% with melanomas of 1.51 to 4.00 mm and to 34.4% with melanomas >4.01 mm in thickness.[49] Cascinelli and colleagues reported similar results in an analysis of 1,108 patients with stage IB or II melanoma. Among patients with melanomas of 1.01 to 2.00 mm, as in the case study discussed here, 8.1% had a positive SLN.[50]

Rousseau and associates performed an extensive analysis of 1,375 patients undergoing SLNB and found that the 6th Edition of the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma accurately predicted SLN positivity in clinically node-negative patients.[52] In their analysis, the incidence of SLN metastasis was 11% in patients with non-ulcerated primary melanomas that were 1.01 to 2.00 mm thick, increasing to 22% in patients with an ulcerated primary tumor of similar Breslow thickness. The strongest independent predictors of SLN metastasis were primary tumor thickness and ulceration.[52] Other groups have observed similar results.[53-55] More recently other factors, including high mitotic tumor rate, tumor drainage to multiple nodal basins, younger patient age, and absence of tumor-infiltrating lymphocytes have also been shown to increase the risk of SLN metastasis.[50,55,57]

Assessing Microscopic SLN Tumor Burden

The most important prognostic factors in melanoma patients with lymph node metastases are the number of metastatic nodes and the lymph node tumor burden.[2] The 6th Edition AJCC staging system defines tumor burden in terms of microscopic (clinically occult and detected pathologically) or macroscopic (clinically apparent by physical or radiologic examination).[1] There is a wide variation in 10-year survival rates for melanoma patients with micrometastatic nodal involvement, ranging from 63% for patients with minimal disease (micrometastasis in a single node, no ulceration) to 36% for patients with 2 to 3 microscopically involved nodes and an ulcerated primary.[1] This prognostic heterogeneity can complicate therapeutic options and cause confusion for both clinicians and their patients.

In the hope of providing more useful classifications for patients with micrometastatic stage III disease, a number of researchers have tried to use SLNB data to refine the assessment of tumor burden. The various criteria that have been examined are depicted in **Figure 6**.

Starz and colleagues proposed a staging concept for SLN metastases based on the number of 1-mm slices with detectable melanoma cells and the centripetal depth of spread (in mm) of tumor cells from the lymph node capsule into the interior of the lymph node.[58] The lowest classification, S0, had no detectable tumor cells, whereas the highest classification, S3, had more than 2 1-mm slides with melanoma cells covering a distance of >1 mm from the SLN capsule to the interior of the node. Higher S classifications were significantly associated with an increased risk of non-SLN metastases and distant metastases,[58] indicating that increased micrometastatic tumor burden is of prognostic importance.

A different system of measuring tumor burden was proposed by Dewar and associates in their analysis of 146 patients with SLN metastasis, which focused on the microanatomic location of tumor cells within the sentinel node.[59] Patients with extensive (any metastasis larger than 5 mm or any node with extracapsular spread) or multifocal (multiple discrete deposits) metastases were significantly more likely to have non-SLN involvement than patients with subcapsular (confined to subcapsular sinus) or combined (subcapsular and parenchymal) metastases. Subcapsular metastases were associated with a particularly favorable prognosis: none of the 38 patients with only subcapsular metastases had positive non-SLNs.[59] Hence, the amount of microscopic tumor burden in the SLN and its location in the SLN appear to be important prognostic factors for recurrence and non-SLN involvement.

Currently, most melanoma patients diagnosed with lymph node metastasis have microscopic disease, and many of these have a very small tumor burden. Yet, these patients are grouped together in the 6th Edi-

tion AJCC staging system as N1a or N2a disease, with a great variability in 10-year survival from 63% to 36%.[1] At M. D. Anderson Cancer Center, we were interested in evaluating whether the current AJCC staging system accurately predicts survival in patients with a small amount of SLN microscopic tumor burden. We evaluated, in a comprehensive manner, the impact of SLN tumor burden on recurrence and survival in 359 patients with SLN metastasis.[60,61] Regardless of the measure of microscopic tumor burden employed (largest diameter, square area, number of foci, or location), higher levels of tumor burden were associated with increased recurrence rates and decreased survival rates. Other factors that affected recurrence-free and disease-specific survival in SLN-positive patients were the Breslow thickness, ulceration of the primary tumor, and the total number of positive nodes. Through multivariate analysis and risk modeling, we were able to identify a population of low-risk patients who had no ulceration of the primary tumor, 1 or 2 positive lymph nodes, and an SLN focus of ≤2 mm. This low-risk group, which had a 10-year survival rate of approximately 90%, is not currently represented by the stage III survival curves in the current AJCC staging system.[60,61]

Figure 6. SLN Tumor Burden Measurements

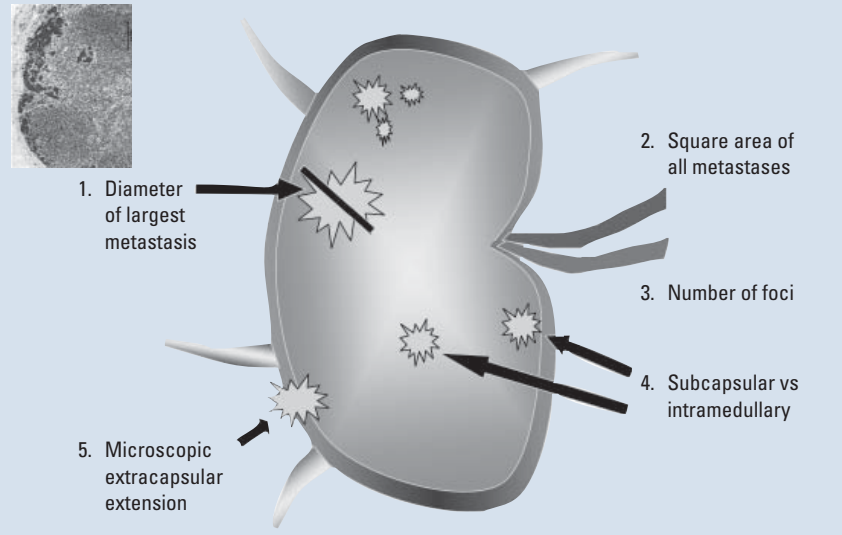


Illustration courtesy of Robert H. I. Andtbacka, MD, CM, FRCS(c).

Case Continued

SLNB is performed and 1 SLN is identified. Histopathologic analysis (H&E and IHC staining) indicates the presence of a single cluster of subcapsular metastatic cells with a diameter of 0.2 mm in the SLN. What would you recommend next for this patient?

1. Nodal observation
2. Staging work-up with an MRI of the brain and a CT scan of the chest, abdomen, and pelvis followed by nodal observation, if the work-up is negative for distant metastatic disease.
3. Staging work-up with an MRI of the brain and a CT scan of the chest, abdomen, and pelvis before a completion lymph node dissection (CLND) is performed.
4. CLND and a staging work-up with an MRI of the brain and a CT scan of the chest, abdomen, and pelvis.

The faculty recommends that the patient undergo CLND (choice #4). Although the focus of metastatic disease is small, this patient should still be considered node positive. Her nodal stage is N1a (micrometastatic involvement of 1 node) and she is clinical stage III (regional disease) and pathologic stage IIIA (T2a and N1a).[1] Studies of patients with micrometastatic SLN involvement (clinically negative regional lymph nodes but a positive SLN as determined by biopsy) find that approximately 16% will have involvement of a non-SLN.[11,62] As described in the subsequent section, there is great interest in identifying a subset of low-risk patients who may not require CLND. Until more data are available, however, the 7th Edition AJCC Melanoma Staging Subcommittee has concluded that there is no safe threshold of tumor burden that can be defined at this time (CM Balch, personal communication). Because this patient is SLN-positive, she should undergo CLND or enroll in a clinical trial as per NCCN guidelines.[5] A staging work-up with an MRI of the brain and a CT scan of the chest, abdomen, and pelvis or CT-PET scan is also recommended. However, this work-up is not necessary before a CLND is performed, since the risk of radiographically detectable synchronous distant metastases is less than 2%.[63]

Management of Micrometastatic Disease

The optimal management of micrometastatic disease continues to be an area of controversy in patients with melanoma. Although NCCN guidelines recommend CLND for patients with a positive SLN,[5] a recent study of US practice patterns found that only 50% of patients with SLN metastases underwent a CLND.[64] Patients older than 75 years with a thin (≤1 mm) primary melanoma or with a primary tumor on a lower extremity were significantly less likely to undergo CLND.[64]

CLND in patients with micrometastatic disease. Part of the dichotomy between treatment guidelines and practice may be due to uncertainty regarding the impact of SLN biopsy and CLND on patient outcome. The Multicenter Selective Lymphadenectomy Trial (MSLT) attempted to address the impact of SLNB on outcome by randomizing patients with intermediate-thickness primary melanoma and clinically negative regional lymph nodes to 2 treatment groups: (1) wide local excision of the primary melanoma and nodal observation, with lymphadenectomy if nodal relapse occurred; or (2) wide local excision of the primary melanoma and SLNB followed by immediate CLND for patients with positive SLN.[65] There was no significant difference between the 2 treatment groups in 5-year survival rates. However, in the subgroup of patients with nodal metastases, immediate lymphadenectomy following SLNB resulted in significantly higher 5-year survival rates than delayed lymphadenectomy following observation (72.3% vs 52.4%; P=.004).[65] These data thus indicate that, in patients with nodal involvement, immediate CLND is associated with improved survival.

Nevertheless, fewer than one-fifth of patients with micrometastatic disease in the SLN will have non-sentinel node involvement.[11,62] If patients at lowest risk for non-sentinel node involvement could be identi-

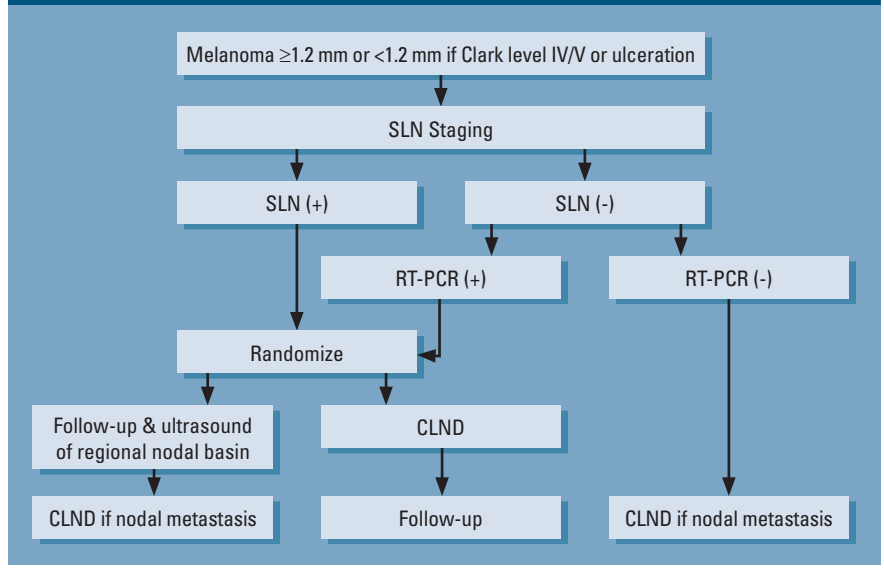
Table 3. A Working Model for Assessing Risk of Non-SLN Involvement in Patients With a Positive SLN

Factor	Score
Tumor thickness	
≤ 2 mm	0
> 2 mm	1
Largest SLN metastatic focus	
≤ 0.5 mm	0
> 0.5 to ≤ 2 mm	1
> 2 to ≤ 10 mm	2
> 10 mm	3
Number of SLNs harvested	
≥ 3	0
2	1
1	2

The sum of the scores for each factor determines overall risk, with the lowest scores representing the lowest risk.

Source: Gershenwald JE et al. *J Clin Oncol.* 2008;26:4296-4303.[70]

Figure 7. Design of the Multicenter Selective Lymphadenectomy Trial II



CLND, completion lymph node dissection; RT-PCR, reverse transcriptase-polymerase chain reaction; SLN, sentinel lymph node.

More information is available at www.clinicaltrials.gov/show/NCT00297895.

fied, they could potentially be spared CLND without an adverse impact on outcomes. The ability to identify such a subgroup, however, is a hotly debated topic. The prognostic significance of isolated tumor cells (ITCs) in the SLN is a particularly controversial area (see the sidebar on page 13). As new technology continues to expand the current limits of detection of melanoma cells, the issue of the prognostic significance of micrometastatic disease becomes increasingly important. Although the AJCC 7th Edition recommends that patients with histologically-detected micrometastatic disease (by H&E staining, IHC staining, or both) be considered node positive, disease detected by molecular methods does not meet this criteria. Current attempts to stage melanoma with molecular probes, such as reverse transcriptase polymerase chain reaction (RT-PCR) analyses of melanoma-specific mRNA, have not yet demonstrated the ability to yield useful prognostic information.[17]

A potential confounding factor in the assessment of outcomes in patients with micrometastatic disease is the likely therapeutic benefit of SLNB and CLND.[66] The excellent outcomes reported in certain subgroups of patients with micrometastatic SLN involvement could reflect the removal of metastatic disease by the diagnostic procedures. The question then becomes whether the outcomes are a result of the procedures, or whether certain patients would have excellent outcomes without the procedures. Another potential problem in assessing studies of micrometastatic disease is the short follow-up time of some reports. Very small metastatic deposits may take long periods of time to cause disease recurrence.[66]

Identifying patients at low risk of non-sentinel lymph node involvement. Factors that correlate with a reduced likelihood of non-sentinel node involvement include low nodal tumor burden or number of metastatic foci[16,58,62,67,68] and subcapsular microanatomic tumor location.[59] On the basis of these studies, it has been suggested that patients with micrometastatic foci <0.1 mm and patients with only a single micrometastasis may be spared CLND.[16,67] However, other studies have been unable to identify criteria that accurately predict non-SLN involvement.[15,69] These authors thus recommend that CLNDs continue to be performed on all SLN-positive patients.

A study at the M. D. Anderson Cancer Center in Houston, Texas, evaluated the effect of tumor burden and other parameters on non-SLN involvement in patients who had microscopic nodal involvement as identified by SLNB.[70] SLNB in 2,203 clinically node-negative patients revealed that 359 (16%) were SLN positive. Of these patients, 343 underwent a CLND and 48 (14%) were found to have non-SLN involvement. Multivariable logistic regression analysis identified measures of tumor burden as the most significant independent prognostic factors for positive non-sentinel nodes. Tumor thickness of more than 2 mm and the number of SLNs harvested during biopsy were also predictors of non-sentinel node involvement. A working model to predict the risk of positive non-SLNs was developed on the basis of these data (**Table 3**).[70] This model successfully distinguished low-risk patients from high-risk patients: the rates of non-sentinel node involvement were 0%, 4.0%, 22.2%, and 46.7% in patients with total scores of 0, 1 to 2, 3 to 4, and 5 to 6, respectively. The authors caution, however, that before CLND can be safely eliminated in low-risk groups, prospective clinical trials will be required to assess the impact of such a change on patient outcome.[70]

Future Directions in Micrometastatic Disease

Data from the MSLT II trial may help clarify the role of CLND in patients with micrometastatic disease and provide further insights into the potential utility of molecular staging of melanoma.[71] In the MSLT II trial, clinically node-negative patients with primary melanomas ≥1.2 mm thick, or <1.2 mm thick with ulceration or with Clark level IV/V, are stratified into SLN-positive and SLN-negative cohorts, as determined by SLNB and H&E and IHC staining (**Figure 7**).

SLN-positive patients will be randomized into 2 groups: (1) CLND or (2) follow-up and ultrasound of the regional nodal basin, followed by CLND if nodal metastases are detected. This part of the trial will test whether there is a survival difference in patients with a positive SLN who undergo immediate CLND versus delayed CLND if they develop regional metastatic disease while being followed by ultrasound. Subgroup analyses may also be able to identify characteristics associated with a low risk of non-sentinel node involvement. SLN-negative patients will have nodal tissue analyzed by RT-PCR. RT-PCR-negative patients will be followed and will undergo CLND if nodal metastasis occurs. RT-PCR-positive patients will be randomized to immediate CLND or follow-up with ultrasound of the regional nodal basin followed by CLND if nodal metastases are detected. This arm of the trial will evaluate the prognostic significance of molecular markers of disease, and establish whether early intervention in patients with molecular, but not histological, evidence of disease can change patient outcomes.

The European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group is also planning a trial to examine the impact of CLND in patients with minimal SLN tumor burden. In this registration study, patients will be divided into an arm receiving CLND and an arm receiving nodal observation only on the basis of patient preference. One of the goals of this trial is to assess whether or not CLND improves the survival of patients with SLN submicrometastatic foci <0.1 mm in diameter.[72]

Conclusion

An extensive body of data supports the prognostic significance of SLN involvement in patients with melanoma. Although a minority of patients with stage I or II melanoma will be SLN positive, regional lymph node involvement remains the most important prognostic factor in these patients; as such, knowledge of nodal status is a key factor in guiding treatment decisions. As our methods for detecting nodal tumor cells has improved, the potential existence of a lower threshold for tumor burden limit has become an area of controversy. Some studies indicate that even very small deposits of tumor cells are associated with poor patient outcomes, but others disagree. Data from ongoing trials, such as the MSLT-II, may help answer these questions. Until that time, however, clinicians should adhere to the guidelines of the new 7th Edition of the AJCC staging system for melanoma, which clarifies that there is no lower limit for tumor burden as determined by H&E or IHC staining. All nodes with histologically detectable metastases should be considered positive, and the patients should be staged as having regional disease and a CLND recommended unless the patient is enrolled into a clinical trial such as MSLT-II.

The Prognostic Impact of ITCs: Controversies and Considerations

SLN biopsies sometimes reveal ITC in sentinel nodes. An important issue in staging is whether these cells are sufficient to stage the patient as SLN positive. Some clinicians disregard such findings, citing lymph node micrometastases in breast cancer as a precedent. For breast cancer, the patient is classified as pN0(i+); the presence of ITC is noted in the pathology report, but the patient is considered to be N0 (no regional lymph node metastasis).[13] This classification is supported by a recent study in which the overall and recurrence-free survival rates in breast cancer patients with nodal ITC were similar to those in patients with no nodal involvement.[14]

The issue of the importance of ITC in melanoma, however, remains controversial. The biology of melanoma is different from that of breast cancer, and studies of ITC in melanoma are divided on the prognostic importance of this finding. Scheri and colleagues recently reported their experience with 57 patients with ITC, defined as melanoma cell clusters ≤0.2 mm in diameter.[15] Fifty-two of these patients underwent a CLND, and 6 (12%) had additional involved lymph nodes. Compared to patients with tumor-negative SLNs, patients with ITC had significantly lower rates of disease-free survival (83% vs 61%; *P*=.0008) and melanoma specific survival (87% vs 80%; *P*=.02) at 10 years, indicating that ITC were prognostically important. The authors concluded that "Patients with ITC should be considered for CLND."[15] Unpublished findings from the M. D. Anderson Cancer Center support this recommendation (JE Gershenwald and MI Ross, personal communication, November 2008).

Other researchers have concluded that very small metastatic foci do not impact patient outcome. Govindarajan and colleagues reported that 0 of 13 patients with SLN tumor deposits ≤0.20 mm had a positive CLND, and that none of these patients experienced a recurrence during a median follow-up of 31.2 months.[68] van Akkooi and colleagues evaluated outcomes in 16 patients with submicrometastases (clusters of more than 10 cells, but <0.1 mm) and found that none of the patients had positive non-SLN, and that their overall and disease-free survival rates were comparable to SLN-negative patients.[16] A subsequent analysis of patients in the EORTC melanoma database confirmed these findings.[73] An assessment of IHC-positive cells by Satzger and colleagues found that patients with ITC, defined as clusters of no more than 2 cells, had a prognosis similar to that of SLN-negative patients.[74] In contrast, those with micrometastases (defined as clusters of at least 3 melanoma cells) had higher rates of relapse and melanoma-related death.[74]

There are several important issues that should be considered in the interpretation of these studies. Most of the studies use different definitions for ITC, so it is difficult to compare their results. In addition, many of these studies report relatively short-term follow-ups. This is a particular issue when assessing ITC, as lead time bias is a potential confounding factor: the smaller the metastatic deposit being assessed, the longer it will take to show an impact on outcomes such as recurrence or death. The positive outcome of patients with ITC may also be affected by the therapeutic benefit of SLNB and CLND during these studies.[66] The conflicting conclusions of these studies indicate that further data are necessary to determine the prognostic significance of ITC. Until such data become available, clinicians are advised to follow the upcoming AJCC Melanoma Staging Subcommittee 7th Edition guidelines, which state that there is currently no lower threshold for staging a patient with node-positive melanoma by conventional H&E or IHC staining techniques (CM Balch, personal communication).

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POSTTEST Advances in Melanoma Staging and Surgical Techniques

For each question or incomplete statement below, please indicate your answer or completion in the space provided on the evaluation form on page 16.

1. What are the 2 most powerful predictors of survival in patients with localized melanoma?
- A. Ulceration and Clark invasion level
- B. Tumor thickness and ulceration
- C. Clark invasion level and mitotic rate
- D. Tumor thickness and mitotic rate

2. Histopathologic analysis of nodal tissue by IHC staining should:
- A. Not be used to detect nodal micrometastases
- B. Use at least 1 melanoma-associated marker
- C. Replace H&E staining
- D. Use only the S-100 marker

3. Under the new 7th Edition AJCC melanoma staging criteria:
- A. All patients with melanoma from an unknown primary site should be staged as Stage III
- B. All patients with melanoma from an unknown primary site should be staged as Stage IV
- C. Patients with an unknown primary and an isolated nodal metastasis should be staged as Stage III
- D. Patients with an unknown primary and an isolated skin metastasis should be staged as Stage II

4. In assessing pigmented lesions, multiple incisional biopsies:
- A. Are appropriate when the lesion is large
- B. Are associated with lower mortality rates than excisional biopsies in patients with head and neck melanoma
- C. Should not be used when the risk of melanoma is low
- D. Should be confined to the thinnest part of the lesion

5. The assessment of frozen tissue sections:
- A. Is not performed in Mohs micrographic surgery
- B. May make it difficult to differentiate between melanoma and benign melanocytic hyperplasia
- C. Cannot be performed intraoperatively
- D. Is more sensitive and specific than assessment of permanent sections

6. Patients who are treated with imiquimod should receive:
- A. Twice daily therapy
- B. Concomitant radiotherapy
- C. Concomitant 5-FU
- D. Long-term follow-up

7. In patients with Stage I or II melanoma, the risk of positive SLNs is lowest in those with:
- A. Thin melanomas
- B. Low numbers of tumor-infiltrating cells
- C. High mitotic rates
- D. Ulceration

8. According to data from the M. D. Anderson Cancer Center, higher levels of micrometastatic SLN tumor burden:
- A. Do not affect patient outcomes
- B. Affect patient outcomes only for those with an ulcerated primary tumor
- C. Are associated with increased recurrence rates and decreased survival rates
- D. Are associated with increased recurrence rates but has no impact on survival

9. A patient presents with Stage II melanoma and undergoes SLN biopsy. H&E and IHC staining reveal only ITC in the sentinel node. AJCC 7th Edition guidelines state that this node should be:
- A. Considered negative for metastatic disease
- B. Considered negative for metastatic disease if the foci are < 0.1 mm in diameter
- C. Considered positive for metastatic disease
- D. Re-evaluated with melanoma-specific RT-PCR

10. Confounding factors in the assessment of the impact of micrometastatic disease and ITC include:
- A. Potential therapeutic benefit of SLNB and CLND
- B. Short follow-ups
- C. Differing definitions of ITC
- D. All of the above

EVALUATION FORM Advances in Melanoma Staging and Surgical Techniques

Please use the scale below in answering these questions. Fill in the circle completely. You may use pen or pencil.

	Very low	Low	Moderate	High	Very High

1. To what degree will you apply the following objectives of the educational activity in your practice and/or professional responsibilities?

A. Interpret changes to the latest edition of the AJCC staging system for cutaneous melanoma and extrapolate those changes to clinical practice ❍ ❍ ❍ ❍ ❍

B. Describe different biopsy techniques and identify clinical situations best-suited for each procedure ❍ ❍ ❍ ❍ ❍

C. Evaluate techniques employed in Mohs micrographic surgery and staged excision ❍ ❍ ❍ ❍ ❍

D. Appraise the value of imiquimod as treatment for melanoma in situ ❍ ❍ ❍ ❍ ❍

E. Analyze controversies regarding the use of sentinel lymph node biopsy and the interpretation of biopsy findings ❍ ❍ ❍ ❍ ❍

	Very low	Low	Moderate	High	Very High

2. To what extent were you satisfied with the overall quality of the educational activity? ❍ ❍ ❍ ❍ ❍

3. To what extent was the content of the activity relevant to your practice or professional responsibilities? ❍ ❍ ❍ ❍ ❍

4. To what extent did the program enhance your knowledge of the subject area? ❍ ❍ ❍ ❍ ❍

5. To what extent did the program change the way you think about clinical care and/or professional responsibilities? ❍ ❍ ❍ ❍ ❍

6. To what extent will you make a change in your practice and/or professional responsibilities as a result of your participation in this educational activity? ❍ ❍ ❍ ❍ ❍

7. To what extent did the activity present scientifically rigorous, unbiased, and balanced information? ❍ ❍ ❍ ❍ ❍

8. To what extent was the activity free of commercial bias? ❍ ❍ ❍ ❍ ❍

Posttest Answer Sheet

1. ❑ 2. ❑ 3. ❑ 4. ❑ 5. ❑ 6. ❑ 7. ❑ 8. ❑ 9. ❑ 10 ❑

If you wish to receive credit for this activity, please complete the form below and:

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