Unanswered Questions About Margin Recommendations for Primary Cutaneous Melanoma

Joyce Y. Wong, MD, and Vernon K. Sondak, MD, Tampa, Florida

Key Words
Melanoma, surgery, wide excision

Abstract
Radical wide excision with appropriate margins based on depth of tumor invasion has been the standard adopted in NCCN and national clinical practice guidelines in oncology based on randomized controlled trial data. When carefully scrutinized, however, questions remain unanswered about what constitute appropriate margins in many frequently encountered clinical situations. In addition to the single characteristic of tumor depth, factors such as primary tumor location, histologic classification, and even specific patient characteristics may all contribute to risk for local recurrence, and therefore should potentially be considered in margin recommendations. This article addresses current uncertainty surrounding optimal margin status in primary cutaneous melanoma. (JNCCN 2012;10:357–365)

Medscape: Continuing Medical Education Online

Learning Objectives
Upon completion of this activity, participants will be able to:
• Distinguish current recommendations for surgical margins in excision of melanoma
• Evaluate different methods for the biopsy of melanoma and the role of expert pathologists
• Analyze surgical practices for melanoma
• Assess how to manage nevi among patients with melanoma
Surgical removal remains the mainstay of treatment for primary cutaneous melanoma, and is generally considered one of the most noncontroversial aspects of melanoma management. Because the term wide local excision has no specific meaning nor a corresponding procedural billing code, the authors prefer the term radical wide excision to refer to any surgical procedure for primary melanoma intended to 1) include a minimum measured margin of normal-appearing skin in all radial directions surrounding the melanoma biopsy scar and/or any residual pigmented lesion at that site (wide excision); and 2) extend downward to the level of the investing muscular fascia (radical excision). The current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma (available in this issue and online at www.NCCN.org)\(^1\) and those of Europe\(^2\) and of Australia and New Zealand\(^3\) all recommend 1- to 2-cm excision margins predicated on the Breslow thickness of the primary tumor (Table 1). However, in this era of personalized medicine, it seems evident that factors other than the tumor's thickness should at least be considered in surgical decision-making.

### Unanswered Questions About Excision Margins

Excision margin recommendations are based on the results of randomized controlled trials conducted in different patient populations comparing various margins. Most surgeons accept these recommendations at face value, rarely considering the many situations in which questions remain. Recognizing these questions may prompt retrospective or prospective studies to better answer them, and perhaps permit true personalization of surgical recommendations.

#### Should Margin Recommendations Differ Based on Nodal Status?

Virtually all prospective studies excluded patients with clinically evident nodal metastases, and none were conducted in patients staged using sentinel lymph node biopsy.\(^4,5\) None were adequately powered to detect small but potentially clinically significant differences in local recurrence or mortality rates, and in fact no study has ever shown a difference between the narrow and wide excision arms for either of these end points.\(^6\) Moreover, these underpowered studies had virtually no ability to identify subsets of patients at higher risk for recurrence with narrower margins. Locoregional recurrence is likely to be substantially greater in node-positive patients, especially those with macroscopic node-positive disease. This is only one example of a relatively commonplace scenario in which legitimate questions can be raised about available guideline recommendations; others abound.

#### How Much of an Increase in Local Recurrence or Death is Justifiable to Avoid a Split- or Full-Thickness Skin Graft for Melanomas 1 to 2 mm in Thickness?

Treatment recommendations for melanomas 1 to 2 mm in thickness remain vague, with narrower margins recommended when they would permit primary closure.\(^1,6\) Local recurrences were numerically more common with 1-cm margins in at least one trial.\(^4\) Studies have found that full-thickness skin grafts procured from the sentinel node biopsy site provide an excellent cosmetic result and decrease the need to compromise on margin width in melanomas of intermediate thickness.\(^10\)

#### Might Excision Margins Larger Than 2 cm Be Associated With Lower Recurrence Rates for Thick Melanomas, Particularly Those With Angiolymphatic Invasion or Gross or Microscopic Satellitosis?

No randomized trial has specifically evaluated melanomas thicker than 4 mm, and virtually all trials have excluded melanomas with clinically evident

| Table 1 Current Guidelines for Excision Margins in Primary Cutaneous Melanoma |
|-----------------------------|------------------|
| Melanoma Depth               | Margin Recommendation |
| **NCCN**\(^1\) and ESMO\(^2\) Guidelines |                  |
| Melanoma in situ            | 0.5 cm           |
| < 1 mm                      | 1 cm             |
| 1.0-2.0 mm                  | 1-2 cm           |
| > 2 mm                      | 2 cm             |
| Australian Cancer Network Guidelines\(^3\) |                  |
| Melanoma in situ            | 0.5 cm           |
| < 1 mm                      | 1 cm             |
| 1.0-2.0 mm                  | 1-2 cm           |
| 2.0-4.0 mm                  | 1-2 cm           |
| > 4.0 mm                    | 2 cm             |

Abbreviation: ESMO, European Society for Medical Oncology.
satellite tumors, although these tumors have the highest likelihood of local recurrence. Melanomas 2 mm or larger have been evaluated in prospective trials comparing 1- versus 3-cm and 2 versus 4- or 5-cm margins. Most outcomes were actually the same for patients undergoing narrow margin excisions, suggesting that wider margins did not confer a recurrence-free advantage. Thus, the widest margin recommendation currently is 2 cm for intermediate or thick melanomas, regardless of any other factors.

**Should Melanomas With Ulceration and High Mitotic Count Be Treated With Different Margins Compared With Other Tumors?**

The current AJCC staging of primary tumor status (T status) is based on tumor depth, and subdivided based on presence of ulceration. T1 lesions are further subcategorized based on mitotic count. Both ulceration and a mitotic count greater than 0 are considered poor histologic features and confer significantly worse overall survival but do not currently factor into recommendations for excision margins. Analysis of patients with intermediate-thickness melanoma identified ulceration as a significant predictor of local recurrence, showing a 6.6% recurrence rate with ulceration compared with 1.1% in the absence of ulceration. However, no randomized data are currently available to suggest that margins larger than 2 cm are warranted for ulcerated lesions, irrespective of thickness.

**Why Should Melanoma In Situ Be Treated With a Smaller Margin Than a Thin Melanoma?**

NCCN and other national guidelines recommend 0.5-cm margins for melanoma in situ, but this recommendation is not evidence-based. In fact, studies of lentigo maligna (a specific histologic pattern of melanoma in situ frequently encountered on the head and neck) have consistently shown that approximately 50% of patients with melanoma, especially on the head and neck, required margins greater than 0.5 cm to achieve clearance. Moller et al. routinely used staged excisions to individualize margin width for head and neck melanoma in situ. As initially described by Johnson et al., staged excision, perimeter excision, square procedure, or contoured excision techniques remove a full-thickness strip of tissue 0.5 cm or more beyond the visible edge of pigmentation (sometimes supplemented by Wood lamp examination) for permanent histopathologic analysis. If evaluation of the strips is negative, central excision of the tumor is then performed with reconstruction using a flap or graft as necessary.

This technique allows aesthetic reconstruction and avoids open wounds while reliable permanent sections are performed. Punch biopsy evaluation has been used in a similar fashion to map out areas of extensive melanoma in situ. Importantly, the central excision specimen should also be subject to permanent section analysis to avoid missing a focus of invasive melanoma. On the extremities and trunk, the authors often use a 1-cm margin for typical melanoma in situ, because of the ease of cosmetic closure and relatively high likelihood of failure to clear the melanoma in situ with a 0.5-cm margin. Additionally, although the exact incidence is unknown, discovering foci of invasive melanoma in the excision specimen is a real concern, which would call for a wider margin.

**When Is Mohs an Acceptable Option for Excision of Melanoma In Situ, and How Should It Be Done? Is Mohs Ever an Acceptable Option for Invasive Melanoma?**

Mohs micrographic surgery, traditionally considered contraindicated for invasive melanomas, has been studied in melanoma in situ, particularly in cosmetically sensitive areas such as the head and neck. Using this technique, Bene et al. showed a 95.1% clearance of melanoma in situ with a 2% recurrence rate. The addition of immunostains improved the observed recurrence rate to 0.5% or less. Studies investigating the clinical efficacy of Mohs micrographic surgery in melanoma, however, have been relatively small with limited follow-up. Moreover, despite immunostaining with specific antigens, such as MART-1, differentiating between melanoma in situ and atypical but benign melanocytic proliferations on sun-damaged skin may be very difficult.

**Should Desmoplastic and Acral Lentiginous Melanomas Be Treated With Different Margins Compared With Other Histologic Types?**

Desmoplastic melanoma is a relatively rare melanoma subtype, accounting for fewer than 1% of cases. It exhibits unique clinical characteristics, occurring more frequently in men, elderly patients, and the head and neck region, and tends to present with thicker tumors. Both pure and mixed desmoplastic variants are described. Some retrospective reports suggest that desmoplastic melanomas have a greater...
risk of local recurrence than other histologic types. Quinn et al.\textsuperscript{25} reported on 280 patients with desmoplastic melanomas and observed an 11% local recurrence rate, significantly higher than the contemporaneous rate of 3.2% for other forms of melanoma. Furthermore, the local recurrence rate was 20% for desmoplastic melanomas with neurotropism, compared with 6.8% without neurotropism. Local recurrence was significantly higher when surgical margins were less than 1 cm.\textsuperscript{25,26} More recently, 2-cm surgical margins were compared with 1-cm margins in patients with both pure and mixed desmoplastic melanoma. Local recurrence was more common with pure than with mixed desmoplastic melanomas, and more local recurrences were seen in both groups with 1-cm margins than in those with 2-cm margins.\textsuperscript{27}

The role of adjuvant radiation therapy, although not definitively delineated by randomized prospective trials, has been associated with reductions in local recurrence in some series.\textsuperscript{28,29} In the authors' institutional experience, desmoplastic melanomas with neurotropism or thickness of 4 mm or more are associated with increased local recurrence rates and may benefit from postoperative radiation. Acral lentiginous melanomas may also be associated with higher local recurrence rates, and genetic studies have suggested that molecular abnormalities may extend in melanocytes far beyond the histologically visible edge of the tumor.\textsuperscript{31} Prospective trial data regarding these histologic types are lacking.

**When Should Reconstruction Be Delayed in Head and Neck Melanomas, and What Are the Optimum Reconstructive Techniques?**

Head and neck melanomas are challenging in terms of resection, and particularly reconstruction. Mohs surgery has been advocated as a tissue-sparing method for head and neck melanomas,\textsuperscript{15} but concerns remain that are similar to those mentioned regarding melanoma in situ. Performing delayed versus immediate reconstruction has also been debated, because of concern over positive margins complicating immediate reconstruction. In a review of more than 100 patients with head and neck melanoma who underwent excision with immediate reconstruction, Sullivan et al.\textsuperscript{32} detected a positive margin in 6% of patients. Tumor characteristics significantly associated with positive margins included T4 lesions, presence of ulceration, and excision of locally recurrent tumor. The same authors followed a similar cohort (patients with melanoma of the head and neck who underwent excision by surgical oncologists with immediate reconstruction by plastic surgeons) for an average of 5.2 years. Most reconstruction was performed with adjacent tissue transfer, followed by skin grafting. A local recurrence rate of 2.8% was observed, suggesting that low local recurrence rates can be obtained in selected patients.\textsuperscript{33}

**Should Scalp Melanomas Be Treated Differently From Melanomas at Other Sites?**

Scalp melanomas tend to behave in a more aggressive fashion than other melanomas of the head and neck.\textsuperscript{34} Although the traditional wide excision does not encompass the periosteum of the calvarium, a recent study recommends subperiosteal resection as a way to reduce locoregional recurrence compared with subgaleal resection.\textsuperscript{35} Certainly, this poses a reconstruction challenge, often requiring muscle flaps or other techniques. Small studies suggest that excisions wider than 2 cm may reduce local recurrence.\textsuperscript{36}

**What Is the Optimal Treatment of Subungual Melanoma, and When Should Digit Preservation Be Considered?**

Subungual melanomas are often diagnosed late, and frequently with a small peripheral biopsy that provides limited information about the maximum tumor thickness and other pathologic prognostic factors. The role of amputation versus digit preservation has been debated, as has the level of amputation, with little or no prospective data available.\textsuperscript{37} A recommendation for amputation at the distal interphalangeal joint for fingers and metatarsophalangeal joint for toes was proposed by O'Leary et al.,\textsuperscript{38} who observed no local recurrences. A recent study advocated amputation of the distal phalanx with a margin of normal-appearing skin.\textsuperscript{39} Moehrle et al.\textsuperscript{40} attempted to determine the role of functional surgery for subungual melanoma, entailing only partial resection of the distal phalanx. When compared with patients who underwent amputation, no difference was seen in recurrence-free survival. Similar data from another study showed no difference in survival between patients who underwent proximal amputation and those who underwent local or distal amputation.\textsuperscript{41} Patients are frequently highly motivated to avoid even partial...
amputation, and subungual melanoma rarely involves the underlying bone. In the authors’ experience, however, the functional results of nail bed excision with skin grafting are generally suboptimal, with many patients reporting persistent problems with sensitivity to light touch and troubling pain with even minor trauma. In comparison, distal phalangeal amputation is usually very well tolerated, with a low incidence of phantom sensations.

How Should a Dermal Nodule of Melanoma Be Treated?
Melanoma can occasionally present without evidence of a primary cutaneous lesion, with the solitary presence of a dermal or subcutaneous nodule. In the absence of an epidermal component, these lesions are often classified as M1a disease (stage IV), but in fact may represent a primary cutaneous melanoma in which the epidermal component has been traumatized, has regressed, or was previously excised and mistaken for a benign nevus. In most retrospective series, solitary dermal melanomas exhibit less-aggressive behavior than cutaneous metastases from known primaries. Lee et al. observed a median survival of 8.3 years in patients with a solitary dermal melanoma, and noted a high incidence of regional nodal disease. Other smaller series showed similar survival rates, and recommended wide excision with 1- to 2-cm margins. Cassarino et al. analyzed dermal melanomas with immunohistochemistry and showed they had lower levels of p53, Ki-67, cyclin D1, and podophyllin staining than cutaneous melanoma metastases. Thus, available evidence suggests that isolated dermal melanoma should be treated as a primary cutaneous melanoma of similar thickness and clinical nodal status, and the authors generally excise them with a 2-cm margin and perform sentinel node biopsy to stage clinically negative regional nodes.

Should Melanomas Arising In a Congenital or Atypical Nevus Be Treated Differently?
Melanomas frequently arise in a preexisting nevus, either congenital or atypical (dysplastic). If the nevus is large, excising the melanoma itself with standard margins may not encompass the entire nevus, and excising the entire lesion with margins appropriate for the melanoma may be excessively disfiguring. Although no prospective data exist, the authors measure the guideline-indicated margins around the melanoma and extend the incision as necessary to also remove the entirety of the residual nevus. If benign nevus cells are present at the margin of excision, they typically conservatively reexcise to a negative margin.

Atypical nevi (without evidence of malignant transformation) are frequently diagnosed using a shave biopsy or other procedure with a positive histologic margin. Although controversial, routine reexcision to negative margins may be unnecessary, with several small-scale studies documenting low short-term recurrence rates and no progression to melanoma. Kmetz et al. evaluated patients with biopsy-proven atypical nevi who were followed up for 5 years or longer. Nearly half had involved biopsy margins. Follow-up showed no occurrence of melanoma. A similar study evaluated 195 dysplastic nevi with mild to moderate atypia with a 2-year follow-up, with a 3.6% local recurrence rate reported, as detected at clinical examination. This was not associated with melanoma.

Both studies support the observation of incompletely excised atypical nevi as an alternative to reexcision. Long-term data are still lacking, particularly for patients with severe or high-grade dysplasia. If patients have multiple atypical nevi, reexcising a few cells at a biopsy margin while numerous other intact lesions are left unperturbed seems difficult to reconcile. Conversely, if the margin-positive lesion was the only one of its kind, conservative reexcision (2–5 mm) would be the authors’ preferred approach.

What Is the Appropriate Excision Margin for Atypical Spitz Tumors and Melanomas Arising in Childhood?
Typical Spitz nevi are considered benign, occurring predominantly in children and rarely in adults. They should generally be completely excised with narrow margins. Atypical Spitz tumors have uncertain malignant potential, and differentiation between Spitz nevi and spitzoid melanoma remains difficult for even the most experienced dermatopathologist. Children younger than 18 years have been excluded from virtually all prospective studies of melanoma excision margins.

Ludgate et al. evaluated 67 patients with atypical Spitz tumors and observed a high (47%) incidence of positive sentinel lymph node biopsies, but only one case of local recurrence in a patient with positive
suspected to be melanoma. Contrary to surgical dogma that shave biopsies are contraindicated in melanoma, most provide appropriate information to guide further treatment. A retrospective study evaluated 600 patients who underwent wide excision after shave biopsy found a melanoma of Breslow depth less than 2 mm. Of these patients, 3% were found to have residual melanoma resulting in a T upstaging, yet only 2% were recommended to have further reexcision and only 1% to undergo sentinel lymph node biopsy not originally indicated based on the biopsy. These data are similar to those from other studies that also showed infrequent change in surgical management in patients diagnosed initially with shave biopsy. Available data suggest that patients referred after shave biopsy diagnosis of melanoma should not be managed differently from those diagnosed with excisional biopsy, even in the presence of a positive biopsy margin.

Should All Patients With Melanoma Undergo Expert Dermatopathology Review Before Surgical Management? Current guidelines recommend that melanoma biopsy reports comment on several histologic features, including thickness, ulceration, and mitotic rate, all of which may impact surgical decision-making. The reproducibility of all these features has been questioned, and available data suggest that expert dermatopathologists may more reproducibly and consistently evaluate them. In a study evaluating this question, an expert panel of dermatopathologists reviewed more than 1200 biopsies of pigmented lesions, altering diagnosis in 27%, with overdiagnosis of nevi and underdiagnosis of melanoma in 14% and 11%, respectively. Santillan et al. reviewed 420 patients with thin melanomas (≤ 2 mm or melanoma in situ) seen in a multidisciplinary melanoma clinic, with expert dermatopathology review in all cases, and noted an overall 4% discordance rate in actual diagnosis when compared with the referring pathologist’s report. Tumor staging was changed in 24%, and a change in margin recommendation was made in 12%. Similarly, McGinnis et al. evaluated more than 5000 primary melanocytic lesions seen in a pigmented lesion clinic, and reported an 11% discordance rate between the expert and initial pathology reviews, with upstaging of 5% of patients. Evaluation of 257 wide excision margins also resulted in a change from clear margin to involved margins. Margins of 1 cm were recommended. The authors treat all atypical and malignant lesions in young children (< 14 years) with a 1-cm margin, regardless of measured thickness, and have not seen any local recurrences. Older children and young adults are treated with margins based on thickness as per the NCCN Guidelines for Melanoma (available in this issue and online at www.NCCN.org). The prognostic significance of sentinel lymph node micrometastasis in pediatric melanoma is not entirely clear, leading some to conclude that sentinel node biopsy is not indicated in atypical Spitz nevi and pediatric melanoma. The authors believe that the procedure provides beneficial staging information and may help clarify the metastatic potential of atypical Spitz nevi and pediatric melanomas. In the authors' practice, sentinel lymph node biopsy is routinely used for lesions 1 mm and larger in thickness in cases of childhood melanoma or when melanoma cannot be excluded, and node-positive cases are managed in a manner fully analogous to that for adults.

The Impact of Biopsy Techniques and Dermatopathology Review on Excision Margin Recommendations

Given the critical role of histopathologic features of the primary melanoma determined from the primary biopsy specimen in surgical decision-making, biopsy techniques may potentially impact treatment. In addition to the biopsy specimen itself, the expertise of the pathologist reviewing that specimen could also influence treatment. Guidelines addressing the surgical management of primary cutaneous melanoma sometimes, but not always, address these issues, and unanswered questions remain.

Should Patients Diagnosed With Shave Biopsy Be Managed Differently From Those Diagnosed With Excisional Biopsy?
The American Academy of Dermatology recommends excisional biopsy with narrow margins for all cutaneous lesions suspected to be melanoma. Narrow excisional biopsy is the most complete method of biopsy, without excessively compromising future wider excision or disrupting lymphatic drainage if sentinel lymph node biopsy proves to be indicated. In practice, however, patients often undergo shave biopsies of lesions that prove to be melanoma, most often because the lesion was not
Unanswered Questions About Margins in Melanoma

Marginal in 6.2%. The authors believe strongly that, whenever practical, expert pathology review should be performed before excision margins and sentinel lymph node biopsy are recommended.

Conclusions

Excision margins for melanoma are widely considered to be well established based on prospective randomized trial data, although available data are not as definitive as they might seem. Many common clinical scenarios pose questions not addressed by available high-level evidence. Room for individualization of surgical recommendations still exists for many patients with melanoma, and future prospective trials are needed to address the areas in which questions remain.

References


CME Activity: Surgical Treatment for Melanoma

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 70% passing score) and earn continuing medical education (CME) credit, please go to www.medscape.org/journal/jnccn.

Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered on Medscape.org, please click on the New Users: Free Registration link on the left hand side of the website to register.

Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net.

American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the U.S. as evidence of participation in CME activities. For further information on this award, please refer to http://www.ama-assn.org/ama/pub/category/2922.html. The AMA has determined that physicians not licensed in the U.S. who participate in this CME activity are eligible for AMA PRA Category 1 Credits™. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the U.S., please complete the questions online, print the AMA PRA CME credit certificate, and present it to your national medical association for review.

1. Your patient is a 50-year-old woman who is referred to you for treatment after a shave biopsy of a nevus on her scalp was labeled as melanoma. You lack other important information regarding this tumor. What are the current recommendations for surgical margins for primary cutaneous melanoma?
   A. 0.5 cm
   B. 1–2 cm
   C. 4 cm
   D. Margins should be determined after the mitotic count of the tumor is established

2. What should you consider regarding the biopsy specimen of this patient's melanoma?
   A. Only excisional biopsy is acceptable to diagnose melanoma
   B. Biopsies for suspected melanoma should have surgical margins of at least 1 cm
   C. Melanoma diagnosed by shave biopsy mandates surgical margins of 2–3 cm at excision
   D. Expert pathology review can alter tumor staging and the margin recommendation

3. As you prepare to treat this patient's melanoma with surgery, which of the following statements regarding this practice is most accurate?
   A. In general, 4- to 5-cm margins are associated with a lower recurrence rate vs. standard margins
   B. Ulcerated lesions should mandate margins of 3–4 cm
   C. Desmoplastic tumors are at lower risk for recurrence
   D. Tumor location on the scalp should prompt consideration of more aggressive excision

4. The patient's melanoma appeared to arise from a nevus. She also has an atypical nevus present on her right forearm, with atypical nevi cells present at the margin of the shave biopsy. What should you consider regarding management of these nevi?
   A. The scalp nevus should be excised during excision of the melanoma
   B. The scalp nevus may be left intact and monitored for growth every 3 months
   C. The forearm nevus should be completely excised with 1-cm margins
   D. It is unreasonable to observe the forearm nevus without further intervention

Activity Evaluation

1. The activity supported the learning objectives.
   Strongly Disagree 2 3 4 5
   Strongly Agree

2. The material was organized clearly for learning to occur.
   Strongly Disagree 2 3 4 5
   Strongly Agree

3. The content learned from this activity will impact my practice.
   Strongly Disagree 2 3 4 5
   Strongly Agree

4. The activity was presented objectively and free of commercial bias.
   Strongly Disagree 2 3 4 5
   Strongly Agree

To obtain credit, visit Medscape online at http://www.medscapecme.org/journal/jnccn.