



Proper management of patients with biopsy-proven melanoma is vitally important. Patients with melanoma in situ, invasive melanoma <1 mm thick, and invasive melanoma >1 mm thick should have surgical resection margins of 5 mm, 1 cm, and 2 cm, respectively. All patients with melanomas >1 mm should be offered a sentinel node procedure, the most important prognostic variable in this group of patients. All patients with metastatic melanoma in the sentinel node should undergo a complete therapeutic lymphadenectomy.

Key words: melanoma, margin of resection, sentinel node biopsy

Cutaneous Melanoma, Part Two: Management of Patients with Biopsy-Proven Melanoma

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Introduction

In part one, the etiologic factors, assessment tools for pigmented nevi, and biopsy techniques were reviewed. The true thickness of the melanoma will contribute to the patient's prognosis and dictate appropriate surgical management. This part will address the management of patients with biopsy-proven melanoma, including appropriate resection margins, the sentinel node hypothesis, and therapeutic lymph node dissections.

Preoperative Evaluation for Patients with Biopsy-Proven Melanoma

A detailed history should include personal and family history of skin malignancies as well as personal history of sun exposure, including time spent in the sun as a child and adolescent, number of blistering sunburns, and frequency of tanning bed use. The physical examination should include a thorough evaluation of the lymph node basins with attention paid to the basins that potentially drain the patient's primary melanoma site. The patient should also have a chest x-ray and liver function test to include lactic dehydrogenase (LDH) as per the National Comprehensive Cancer Network (NCCN)¹ guidelines. There is no role for total body staging studies for patients who do not have any evidence of lymph node spread or distant organ involvement.¹

Margins of Resection

Historically, the resection margin for patients with melanoma has been a circumferential 5 cm margin. However, the traditional dogma of 5 cm margins was based upon pathologic studies where dermal and/or subcutaneous metastases were included in the 5 cm margin of resection.²⁻⁵ These metastases do not require an en-bloc resection and can be managed with a separate incision.

Because 5 cm margins were felt to be excessive, prospective randomized trials were designed to prove that smaller margins were equally effective. The World Health Organization melanoma program performed a randomized, prospective clinical trial^{6,7} comparing excision margins of 1 cm and 3 cm in 612 patients with primary melanomas ≤ 2 mm in thickness. First reported in 1988 and then updated,^{6,7} the disease-free and overall survival rates were similar, as were the incidences of distant, regional, and in-transit metastases in both groups. Local recurrence developed in six patients (0.9%), five in the narrow margin group and one in the wide margin group. As a result, it can be definitively stated that melanomas > 1 mm thick are adequately treated with 1 cm margins. Some have argued that the trial did not resolve the question for melanomas 1–2 mm thick and have suggested that a 2 cm margin might be a reasonable compromise to improve local control.^{8,9}

The Intergroup Melanoma Commit-

tee conducted a prospective, randomized trial in 486 patients with intermediate thickness melanomas (1–4 mm) of the trunk and proximal extremities, comparing resection margins of 2 cm and 4 cm.¹⁰ With a median follow-up of six years, the distant (2 cm–10%, 4 cm–8.5%, *P*=NS) and in-transit (2 cm–2.5%, 4 cm–2.1%, *P*=NS) relapse rates were similar for both groups. The overall five-year survival rates were also similar: 79.5% for 2 cm margins and 83.7% for 4 cm margins (*P*=NS).

In summary, for patients with melanoma ≤1 mm in Breslow thickness, 1 cm circumferential margins are indicated. For patients with 1–2 mm Breslow thickness, 1 or 2 cm circumferential margins are indicated. For patients with 2 mm or greater Breslow thickness, 2 cm margins are indicated. There is no indication for any greater margin than 2 cm in any melanoma patient (Table 1).

Lymph Node Basin Management Sentinel Node Hypothesis and Technique

Until recently, the management of the regional lymph nodes in cutaneous melanoma patients without clinical lymphadenopathy has been controversial. For patients without palpable lymphadenopathy, some investigators proposed removal of all the regional lymph nodes (elective lymph node dissection [ELND]). Proponents of ELND cite nonrandomized trials suggesting improved survival after elective ELND.^{11,12} Opponents object to the significant morbidity of the operation and cite three randomized trials showing no

overall survival benefit.^{13–15} Fortunately, the controversy has been laid to rest with the development of a less morbid, more accurate method to stage the regional nodal basin: intraoperative lymphatic mapping and sentinel lymphadenectomy (LM/SL).¹⁶

The concept of lymphatic mapping formed in the late 1970s as investigators sought ways to determine the lymphatic basin at risk for patients with truncal melanomas using radiopharmaceuticals injected around the primary melanoma site.^{17–19} The concept of the sentinel node (SN) was based on the fact that the lymphatic channel draining a primary melanoma will lead directly to the first lymph node, the sentinel node, in the regional lymphatic basin. This draining lymphatic channel can potentially carry malignant cells from the primary tumour to the SN. Thus, the SN is the lymph node most likely to harbour metastatic disease if a regional nodal metastasis is present.

The most common method for performing LM/SL is performed using a combined technetium-99m sulfur colloid (Nicomed Amersham Canada Ltd., Oakville, ON) and isosulfan blue dye technique (Lymphazurin, Hirsch Industries, Inc., Richmond, VA), and has been well described.^{20–24} To review, patients are brought to the Nuclear Medicine Department approximately three hours prior to surgery for an intradermal injection of filtered technetium-99m sulfur colloid around the primary melanoma site or biopsy scar. Using a large field-of-view gamma counter, dynamic scans of all lymphatic basins at risk for metastatic disease are performed beginning 5 to 10 minutes after the injection. Once the lymph node basin at risk is identified, the area is marked on a hard copy of the lymphoscintigram and sent to the operating room with the patient.

In the operating room, 0.5–1.5 mL of isosulfan blue dye is injected intradermally around the patient's primary melanoma or previous biopsy site. The nodal basin(s) identified on preoperative lymphoscintigram is scanned with a commercially available hand-held gamma detection probe. The area with

the greatest number of counts per second is located and an incision is made. Careful dissection is performed to identify all blue-stained SN as well as radioactive SN. A radioactive SN is defined by a 10:1 ratio of the ex vivo SN counts per second to the residual nodal basin background counts per second. If the ratio is less than 10:1 after removal of the SN, this suggests additional radioactive nodes are present, and the dissection is continued to identify and remove all additional SN. If hot spots have been identified in multiple nodal basins on preoperative lymphoscintigraphy, the above procedure is repeated for each identified nodal basin.

Histologic Validation of LM/SL

Early critics of LM/SL felt the technique may simply be a sophisticated histopathologic technique (step sectioning of the lymph node, immunohistochemical stains) applied to the SN, leading to an increased rate of detecting nodal metastases. The question is, does the SN have true biologic significance or is it simply the product of a sophisticated histopathologic process?^{20,25,26} To validate the SN hypothesis histopathologically, if a nonsentinel node is removed, it must be examined with a similar and sensitive histopathologic technique as the sentinel node.

Each SN was evaluated by frozen-section examination using routine hematoxylin-eosin (H&E) staining and by permanent section examination using H&E and immunohistochemical (IHC) stains including antibodies to S-100 protein. Nonsentinel nodes were evaluated by permanent section examination using H&E and IHC with multiple immunostains including S-100. In the original feasibility trial¹⁶ LM/SL was performed in 194 lymphatic basins yielding 259 SNs; completion lymphadenectomy yielded 3,079 NSN from the same basins. Forty-seven of 259 (18%) SN had metastases as compared with only two of 3,079 (0.1%) NSN. Thus, the false-negative rate of the procedure was less than 1%. Sophisticated histopathologic techniques, including multiple sections and IHC of both the sentinel and nonsentinel nodes, support the concept that the SN is biologically significant.

Table 1: Margins of Resection for Cutaneous Melanoma

Breslow thickness	Circumferential resection margin indicated
melanoma ≤1 mm thick	1 cm
melanoma 1–2 mm thick	1 or 2 cm
2 mm or greater	2 cm
Note: There is no indication for any margin greater than 2 cm in any melanoma patient.	

Key Points

The incidence of melanoma is on the rise worldwide.

The margins of resection for cutaneous melanoma have changed from the once-recommended 5 cm circumferential margin to either a 1 or 2 cm excision margin of the primary site.

Intraoperative lymphatic mapping and sentinel lymphadenectomy is at present the least morbid, most accurate method of staging the regional nodal basin in cutaneous melanoma patients.

Sophisticated histopathologic techniques support the concept that the sentinel node is biologically significant as it is the lymph node most likely to harbour metastatic disease if a nodal metastasis is present.

Melanoma patients with palpable adenopathy and patients who have metastatic melanoma in their sentinel node should be managed with a therapeutic lymph node dissection.

Therapeutic Lymph Node Dissections

Melanoma patients who present with palpable adenopathy should undergo fine-needle aspiration to confirm metastatic melanoma. Both these patients and patients who have metastatic melanoma in their sentinel node should be managed with a therapeutic lymph node dissection, which is a complete removal of all lymph nodes in the nodal basin. In contrast to ELND it is performed only in patients with biopsy-proven metastatic disease in the regional nodal basin. Therefore, removing all potentially involved nodes with metastatic melanoma represents a therapeutic procedure.²⁷

Conclusion

The incidence of melanoma continues to rise worldwide. All melanoma patients can now be managed with either 1 or 2 cm excision margin of the primary site. For patients who have intermediate thickness or greater melanoma (>1 mm) there are still surgical options. Patients benefit from a less morbid minimally invasive lymph node technique: the sentinel node procedure. For patients with metastatic melanoma in the sentinel node or palpable lymph nodes, a complete therapeutic lymph node dissection should be performed. This approach maximizes a patient's chance for survival.



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