

Surgical Management of Primary Cutaneous Melanoma

Marshall M. Urist, MD

Introduction

Until the early 1970s, the surgical treatment of melanoma was based on the clinical observation that melanoma frequently recurred locally and regionally before distant metastasis appeared. The straightforward conclusion was that tumor cells spread from the primary site to surrounding tissues, then to lymph nodes, and finally to common locations of distant metastasis, including the lung, brain, and liver. The standard recommendation was to perform a wide local excision and regional lymph node dissection.

The observation that prognosis was related to tumor thickness (the vertical growth component rather than the radial extent) led to an intensive analysis of the results of therapy in many institutions. The two key surgical questions focused on the extent of local excision and the value of elective (prophylactic) lymph node dissection. While a great deal of progress has been made in reducing the extent of surgical treatment, several questions remain unanswered and new issues have arisen. The importance of these questions is underscored by the rising incidence of melanoma.

Diagnosis, Staging, And Prognostic Factors

All pigmented skin lesions should be examined for the signs of melanoma. Changes in size, color, contour, or the de-

velopment of ulceration and itching are all associated with melanoma and are indications for biopsy. Because Breslow's tumor thickness is the most important histologic factor in determining prognosis and treatment, the biopsy should be excisional and through to the underlying fat whenever feasible. A 1- to 2-mm margin of surrounding normal skin should be included, but the boundaries should not be enlarged to provide better cosmesis when melanoma is suspected. A larger biopsy incision will unnecessarily enlarge the following wide local excision.

The orientation of the biopsy wound closure should take into consideration a subsequent excision to decrease the necessity for skin grafting and improve cosmesis. Extremity biopsy sites are usually closed in a longitudinal axis. Larger lesions may be sampled with a skin punch placed through the thickest area of the tumor and into the subcutaneous fat. Incisional biopsies do not appear to change the prognosis.¹

A complete pathology report contains a description of the thickness, level of invasion, growth pattern, margin status, dimensions, and presence or absence of ulceration. With this information, the tumor is staged according to the staging system of the American Joint Committee on Cancer. Stage I tumors are defined as having a tumor thickness of 1.5 mm or less. Stage II tumors have a thickness of 1.51 to 4.0 mm. Stage III tumors are greater than 4 mm in thickness or have spread to in-transit sites or regional lymph nodes. Stage IV defines tumors metastatic to distant sites.²

Dr. Urist is Professor and Director of the Division of General Surgery in the Department of Surgery at the University of Alabama at Birmingham.

Table 1
Prognostic Factors Analysis of Localized Melanoma
(Stages I and II)

Analysis	χ^2	P Value
Single-factor analysis		
Tumor thickness	459.14	<0.00001
Ulceration	302.61	<0.00001
Level of invasion	198.96	<0.00001
Sex	73.63	<0.00001
Primary melanoma site	71.90	<0.00001
Pathologic stage	66.11	<0.00001
Age	53.15	<0.00001
Growth pattern	53.05	<0.00001
Multifactorial analysis		
Tumor thickness	123.13	<0.00001
Ulceration	54.24	<0.00001
Primary melanoma site	37.20	<0.00001

Many retrospective analyses have reported on large numbers of patients and provide the basis for multifactorial analyses.³⁻⁶ With this information, estimates can be made of the risk of local recurrence, regional nodal metastasis, distant metastasis, and survival. Table 1 is a list of factors derived from a data base of 8,500 patients.⁷ A mathematical model for predicting outcome in patients with melanoma has been used to develop a table of clinical factors and survival rates (Table 2).⁸ While Breslow's tumor thickness is of primary importance, Clark's level of tumor invasion may provide additional prognostic value for thin level melanomas.^{9,10} Tumor thickness is frequently grouped into thin (<1 mm), intermediate (1 to 4 mm), and thick (>4 mm) categories. This is a convenient way to classify patients. However, it is important

to remember that thickness is a continuous variable associated with an increasingly poor prognosis. Other factors, including ulceration, site, age, and gender, may also be considered when making clinical decisions.

Primary Tumor

From observations made before the turn of the century, melanoma patients were treated with local excisions using a 3- to 5-cm radius around the primary site biopsy scar. This was considered standard treatment up to the early 1970s. Despite this recommendation, some surgeons reduced margins to avoid resection of major anatomic structures and improve cosmesis.

In later observations, it was found that local recurrence rates after narrower excisions were equivalent to rates in pa-

Table 2
Predicted Five-Year and 10-Year Survival Rates From Initial Diagnosis for Patients With Localized Melanoma as Calculated by a Computerized Model of Multiple Prognostic Factors.

Tumor Thickness (mm)	Anatomic Site	Ulceration	Clark's Level	Sex	5-Year Survival Rate (percent)	10-Year Survival Rate (percent)
<0.76	Extremity	—	II	—	99	97
	Extremity	—	Other	—	97	94
	Axial	—	II	—	96	92
	Axial	—	Other	—	91	84
0.76-1.49	Extremity	No	II	—	98	97
	Extremity	No	Other	—	93	89
	Extremity	Yes	II	—	94	91
	Extremity	Yes	Other	—	82	72
	Axial	No	II	—	95	93
	Axial	No	Other	—	85	77
	Axial	Yes	II	—	88	81
	Axial	Yes	Other	—	64	49
1.50-2.49	Extremity	No	—	—	86	81
	Extremity	Yes	—	—	76	69
	Axial	No	—	—	76	67
	Axial	Yes	—	—	61	49
2.50-3.99	Extremity	No	—	Female	80	72
	Extremity	No	—	Male	73	62
	Extremity	Yes	—	Female	74	64
	Extremity	Yes	—	Male	64	51
	Axial	No	—	Female	73	63
	Axial	No	—	Male	63	51
	Axial	Yes	—	Female	65	52
	Axial	Yes	—	Male	53	39
4.00-7.99	—	No	II/III	—	80	73
	—	No	IV/V	—	68	58
	—	Yes	II/III	—	67	57
	—	Yes	IV/V	—	51	38
>8.00	—	—	—	—	43	25

Adapted with permission from Balch et al.⁸

tients undergoing operations with wider margins.¹¹ Retrospective analyses indicated that incidence of local recurrence was related to tumor thickness and similar factors related to survival.^{11,12} In two complementary prospective, randomized trials, it was shown that margins need not be greater than 2 cm for tumors of intermediate thickness.^{13,14} The Melanoma Trial of the World Health Organization also demonstrated that tumors less than 1 mm in thickness could be excised with a 1-cm margin, after which no local recurrences were seen. The results of these studies have shown there is no increase in mortality for patients treated with narrow margins.

Although patients with tumors greater than 4 mm in thickness have a relatively high risk of local recurrence (10 to 20 percent), there is little evidence to support extending the width of local excision beyond 2 cm. Wider excisions may reduce the incidence of local recurrence but are unlikely to have a survival benefit when the risk of preexisting systemic metastasis is so high. Wide local excision is defined as a dissection extending down through the subcutaneous tissues to, but not including, the fascia.¹⁵ In most cases, narrower margins of excision allow primary wound closure using advancement techniques and local skin flaps.

The long-term, disease-free survival of patients who develop a local recurrence is 30 percent, which is significantly lower compared with patients without recurrence.¹¹ These findings do not prove that local recurrence is the cause of this poor prognosis. Local recurrence is believed to be an indication of the high biologic potential for further metastasis and not the source of metastasis. There is minimal information available about patients who undergo excisional biopsy of the primary tumor alone. A recent study by Drzewiecki and Andersson¹⁶ suggests that this is an inadequate form of therapy. Excisional biopsy with a 3- to 5-mm margin is appropriate for in situ melanoma.

Regional Lymph Nodes

Early policies regarding the management of regional lymph nodes were also based on the clinical observation that these nodes were a common site for the first appearance of metastatic tumor. Retrospective analyses of clinical data have shown that there is no survival advantage for elective node dissection when patients have tumors less than 1 mm in thickness because the cure rate from local excision alone is very high. At the other extreme, patients with tumors greater than 4 mm in thickness have a very high incidence of distant as well as local and regional metastasis.¹⁷ As expected the survival of this group was not improved by elective node dissection. It is in the intermediate thickness group (1 to 4 mm) that elective node dissection appeared to be a logical approach because the incidence of regional node metastasis was significantly greater than the incidence of distant metastasis.^{4,18}

Despite this theoretical advantage, two prospectively randomized trials have failed to demonstrate an improvement in survival for elective node dissection.^{19,20} These trials were not designed for detailed subgroup analysis, which might have identified patients who benefited from the operation.

Results from the Melanoma Inter-group Trial have recently been reported and will be published in the near future.²¹ The group of patients younger than 60 years with tumors 1 to 2 mm in thickness did achieve a significantly improved survival after elective lymph node dissection compared with observed patients. This is the first trial that was large enough and stratified to permit subset analysis. The prognosis for patients with regional lymph node metastasis is proportional to the number of involved nodes.^{22,23} The survival for patients undergoing resection of lymph nodes containing clinically occult melanoma is significantly longer than patients who undergo resection of palpa-

bly enlarged nodes.²⁴ This is one rationale for performing elective dissection, although it may be related to lead time bias.

Morton et al^{24,25} introduced the concept of a sentinel lymph node biopsy in 1992. Their early work with cutaneous lymphoscintigraphy demonstrated that the lymph node basins draining from a specific site could be defined by injection of a radionuclide into the skin at the primary site before a wide local excision was performed.²⁶ The scan also indicated bidirectional drainage in some truncal and head/neck melanomas. Studies in laboratory animals and subsequently in humans have shown that there are well-defined pathways from each cutaneous site to a specific regional lymph node or nodes. The value of the sentinel node biopsy technique has been confirmed by investigators in other institutions.²⁷⁻³¹ This has led to the Multicenter Selective Lymphadenectomy Trial, in which patients are randomized to wide local excision alone or wide local excision with selective lymphadenectomy.

Analysis of the sentinel node will identify melanoma metastasis if present. This two-step technique involves the use of lymphoscintigraphy to define the direction and location of the node followed by the injection of a visible blue dye to localize the sentinel node during the biopsy procedure. A hand-held gamma detection probe may also be used intraoperatively to facilitate location of the node and confirm complete resection of the radionuclide-containing tissues.³² Resection of this node and histologic analysis can predict the presence of melanoma metastasis with an accuracy of greater than 96 percent.

There is a significant learning curve to the performance of the dye technique that may be shortened by the use of an intraoperative probe. The sentinel node identification rate should be 80 percent or greater. It remains important to use the dye technique for confirmation of the first draining node because the isotope can ex-

tend further along to secondary nodes.

Patients with negative sentinel nodes are presumed not to have nodal metastasis when multiple histologic sections are examined. Lymph nodes can be examined by frozen section at the time of the biopsy. However, even standard hematoxylin and eosin staining alone will underestimate the presence of metastasis. Immunohistochemical stains including S-100 and HMB-45 should be obtained to achieve the highest detection rate. The accuracy of this technique depends on intact dermal lymphatic channels. Therefore, it may not be reliable after a wide local excision has been performed.

When lymph nodes are obviously involved by physical examination or are found to be positive by biopsy (needle or excision), a full regional node dissection

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should be performed. This procedure will provide the best control of tumor growth in the region. While standard complete dissections are performed in the axilla and inguinal areas, a modified dissection is recommended in the neck because it preserves appearance and function without compromising the completeness of the operation.

The results of regional lymph node dissection can be useful in predicting the overall survival for node-positive patients and in determining eligibility for adjuvant therapy and investigational trials.^{22,23,33-37} Although interferon alpha-2b has recently been reported to increase disease-free and overall survival in patients with regional node metastasis, the benefit was not greater for treating patients with oc-

Table 3
Recommended Margins of Excision and Options for
Management of Regional Nodes in Patients With Primary
Cutaneous Melanoma

Tumor Thickness	Radius of Excision	Options for Lymph Nodes
In situ	0.3-0.5 cm	Observation
<1.0 mm	1 cm	Observation
1.0-2.0 mm	2 cm	Observation, SLNBx, ELND
2.01-4.0 mm	2 cm	Observation, SLNBx
>4.0 mm	2-3 cm	Observation, SLNBx

SLNBx = sentinel lymph node biopsy
 ELND = elective lymph node dissection

cult node metastasis (elective dissections) versus those with clinically apparent lymph nodes (therapeutic dissections).³⁸

Follow-up


Patients with a history of melanoma should be aware of symptoms of recurrence and perform a monthly self-examination to look for signs of local/regional recurrences and lymph node enlargement.^{39,40} There have been few studies to test the value of follow-up schedules. We have recently analyzed the source of detection of recurrence in a series of 195 patients with cutaneous melanoma. In one third of cases, the patient noted a symptom or sign of recurrence prior to a routine visit. In the remaining two thirds of patients, the recurrence was found by the physician (70 percent) or in laboratory/x-ray studies (30 percent). For this reason, patients should be carefully instructed in self-examination and advised to promptly report signs and symptoms of tumor recurrence. The intervals for return office

visits are scheduled as a function of the risk for recurrence. Patients with thicker tumors have earlier recurrences than patients with thin tumors and are therefore seen more frequently during the first three years of follow-up. Periodic computed tomographic or magnetic resonance imaging scanning is not indicated in the asymptomatic patient.

Conclusions

Early recognition and excision of primary cutaneous melanoma is the best method to assure a favorable outcome. Detailed analysis of the primary melanoma biopsy specimen will provide information to accurately predict the natural history of the tumor. From this information, a treatment plan is formulated using the guidelines summarized in Table 3. Additional prognostic factors may be taken into account when making these clinical decisions. Randomized trials have shown that most patients can undergo resection with a 1- to 2-cm margin. The sentinel

lymph node concept has provided new insights into the tumor biology of melanoma and may do so for other malignancies as well. At the same time, the availability of the technique has created many questions that will need to be answered in controlled clinical trials. At present, the technique of sentinel lymph node biopsy should be considered as a staging procedure. Results from elective

lymph node dissection trials indicate that most patients do not benefit from the operation. There may be a survival advantage for patients younger than 60 years with tumors of 1 to 2 mm in thickness who undergo the procedure. Patients with stage III melanoma should now be considered for adjuvant interferon or other clinical trials. 

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