

Primary cutaneous malignant melanoma and its precursor lesions: Diagnostic and therapeutic overview

Matthew H. Kanzler, MD, and Serena Mraz-Gernhard, MD *Stanford, California*

During the past few decades, scientific data relating to melanoma have flourished. New information regarding acquired nevi, dysplastic nevi (atypical nevi), and congenital nevi has given us a better understanding of these precursor lesions and their relationships to malignant melanoma. The roles of laboratory testing, photography, and newer diagnostic tools (eg, epiluminescence) to evaluate patients for melanoma or precursor lesions have fallen under close scrutiny. Traditional surgical therapeutic interventions continue to be replaced by less aggressive protocols based on prospective randomized studies. Many new interventions such as sentinel lymph node procedures are currently being evaluated at research/referral centers around the world. We present clinicians with an evidence-based summary of the current literature with regard to primary cutaneous melanoma, its diagnosis, precursor lesions, and therapy. (J Am Acad Dermatol 2001;45:260-76.)

With a lack of scientific data, the standard of care for treatment of patients with melanoma at the beginning of the twentieth century called for extensive mutilating surgery, local amputation of involved body areas, or both. In the mid-twentieth century, aggressive lymph node dissections were popular in an attempt to control metastatic disease despite the lack of scientific data that such procedures did, indeed, affect the survival of patients with melanoma. The purpose of this review is to present clinicians with an evidence-based summary of the current literature with regard to primary cutaneous melanoma, its diagnosis, precursor lesions, and therapy. All patients cannot be referred to a melanoma center or be enrolled in prospective randomized studies. For the majority of patients who are treated outside these research centers, it is hoped that the following review will allow the clinician to choose diagnostic and therapeutic approaches based on facts as we know them today, rather than making these decisions based on "tradition."

Abbreviations used:

AJCC:	American Joint Committee on Cancer
CT:	computed tomographic
ECOG:	Eastern Cooperative Oncology Group
ELM:	epiluminescence microscopy
ELND:	elective lymph node dissection
LDH:	lactate dehydrogenase
NIH:	National Institutes of Health
SLND:	selective lymph node dissection
WHO:	World Health Organization

PRECURSOR LESIONS

Acquired melanocytic nevi

Common acquired nevi typically appear after 6 to 12 months of age. These nevi enlarge and increase in number in early childhood and puberty. Most common acquired nevi remain less than 5 mm in diameter.¹ Nevi continue to increase in number through the third and fourth decades, and then slowly disappear with age. Fifty-five per cent of adults have between 10 and 45 nevi greater than 2 mm in diameter.² Several studies have been published regarding the prevalence of normal nevi in adults with conflicting results. Whereas Holly et al³ found at least one nevus in virtually all adults, Swerdlow, English, and MacKie⁴ noted that approximately 20% of adult patients have no clinical nevi (>2 mm) whatsoever. Bataille et al⁵ found that 21% of adults had more than 50 nevi, whereas Tucker et al⁶ found that only 10% of 998 controls had more than 50 nevi.

From the Department of Dermatology, Stanford University School of Medicine, and the Division of Dermatology, Santa Clara Valley Medical Center.

Reprints not available from authors.

Correspondence: Matthew H. Kanzler, MD, Santa Clara Valley Medical Center, 751 S Bascom Ave, San Jose, CA 95128. E-mail: kanzlerm@yahoo.com.

Copyright © 2001 by the American Academy of Dermatology, Inc. 0190-9622/2001/\$35.00 + 0 **16/1/116239**
doi:10.1067/mjd.2001.116239

Environmental, genetic, and immunologic factors all play a role in determining the number of melanocytic nevi that will develop in a person.² Nevi in children tend to be concentrated on sun-exposed sites, particularly those sites that are at high risk for sunburn.⁷

Several case-controlled studies have looked at the relationship between the number of benign acquired nevi and the risk for the development of malignant melanoma. Swerdlow, English, and MacKie⁴ compared 180 patients with cutaneous malignant melanoma with 197 control patients and showed that the risk of melanoma is strongly related to the numbers of benign melanocytic nevi. Patients with nevi whose diameter exceeded 7 mm, had color variation, and irregular lateral margins had as high as 54 times the relative risk of developing melanoma compared with patients without nevi. The relative risk of melanoma in patients with more than 50 nevi was 12.1, even in the absence of large diameters, color variation, or irregular borders.

Bataille et al⁵ compared 426 melanoma cases with 416 case-control subjects. Patients with 50 to 100 nevi had a risk for the development of melanoma 3.2 times that of those patients with none to 4 nevi. Those patients with more than 100 total body nevi had a relative risk of 7.7 compared with patients with none to 4 nevi. Weiss, Bertz, and Jing⁸ compared 204 patients with melanoma with 200 control patients. The total number of benign nevi proved to be the most predictive parameter for the development of melanoma, with the relative risk of 14.9 in those patients who had more than 50 nevi. Grob et al⁹ looked at 207 nonfamilial patients with melanoma and who were older than 18 years compared with 295 control patients. The presence of more than 120 nevi less than 5 mm in diameter was associated with a relative risk for the development of melanoma of 19.6 compared with patients having fewer than 10 nevi. The presence of at least 5 nevi larger than 5 mm was associated with a relative risk of 10 as compared with patients without such nevi.

Grob et al⁹ further noted that the association between clinical atypical nevi and nonfamilial melanoma could be explained entirely by the association of melanoma with many nevi greater than 5 mm in diameter. No significant relative risk was found for clinically atypical nevi alone, inferring that the risk for the development of melanoma was dependent on the total number of nevi larger than 5 mm, regardless of whether or not they were clinically atypical. These findings are in direct conflict with a study by Roush et al¹⁰ who looked at 246 cases of patients with melanoma compared with 134 non-melanoma controls. These authors found that

although the relative risk of melanoma in patients with more than 15 nevi was significantly elevated at 1.8, this risk became statistically nonsignificant after adjustment for dysplastic nevi. Furthermore, the relative risk for the development of melanoma in patients with any dysplastic nevi was 7.6, which remained basically unchanged even after adjustment for total nevi.

Another interesting finding by Grob et al⁹ was that nevi on the buttocks were an important risk factor in melanoma with an odds ratio of 10.9 for 5 or more buttock nevi compared with patients with no such nevi. Bataille et al⁵ confirmed that nevi on unusual sites (dorsum of the feet, buttocks, and anterior scalp) were risk factors for the development of melanoma and remained significant even after adjustment for atypical nevi.

Although statistics from different studies vary, evidence supports the association between large numbers of nevi and an increased risk for the development of melanoma. Several possible mechanisms have been suggested for this increased risk.⁴ Persons with many benign nevi have more cutaneous "naevomelanocytes" and therefore have more total melanocytes at risk of undergoing malignant transformation than people with few nevi. Numerous moles might also indicate a greater genetic tendency to form melanoma. In addition, multiple nevi might indicate that previous exposure to environmental agents, such as increased sun exposure, has occurred, thereby independently causing both a large number of moles and an increased risk of melanoma formations. Finally, the hypothesis that melanocytes in nevi are particularly prone to undergo malignant transformation is supported by pathologic studies in which 20% to 30% of malignant melanomas were associated with a benign or dysplastic nevus in histologic contiguity.^{11,12}

In conclusion, the overwhelming majority of evidence indicates that patients with an increased number of benign melanocytic nevi have an increased risk for the development of melanoma. The critical number at which point the relative risk becomes significant likely varies from person to person, depending not only on the number of nevi, but also on other coexisting risk factors (eg, family history, environmental sun exposure). Because 80% of *all* patients have up to 50 benign nevi, a practical "cut-off" number of nevi over which patients might be at an increased risk for the development of melanoma would be 50. The relative risk for the development of melanoma in patients with more than 50 nevi compared with "normal" is impossible to discern from the current literature. The relative risk for these patients has ranged from 3 to 15 when

compared with the relative risk for patients with either no nevi or fewer than 5 nevi. Therefore these reported figures are probably inflated because only approximately 20% of normal people have no nevi. A better control group for these studies would have been patients with 10 to 50 nevi, who account for 55% of the normal adult population. Unfortunately, no data are available using this more appropriate control group.

Dysplastic nevi (atypical nevi)

In 1978, Wallace Clark first described distinctive melanocytic moles present in patients from 6 melanoma families. Clinically, these moles showed variability in size, outline, and color combination. They tended to appear on the upper trunk and extremities and generally occurred in large numbers.¹³ Families with these moles, originally termed the "B-K mole syndrome," were noted to have very high rates of melanoma development. Since Clark's first reported cases,¹³ this familial melanoma pattern has been codified and described under various synonyms including the dysplastic nevus syndrome¹⁴ and the familial atypical mole and melanoma syndrome.¹⁵ Because of ease of use, we prefer, and will use, the terms *dysplastic nevi* and *dysplastic nevus syndrome* in this review.

Dysplastic nevi may be observed in persons with or without melanoma and may be inherited in a familial pattern or occur sporadically. They are usually larger than 5 mm in diameter and are either flat or flat with a raised center ("fried egg"). They are darkly or irregularly pigmented with shades of brown and pink and usually have irregular or indistinct borders.¹ Dysplastic nevi are fairly common, with a prevalence rate as documented by biopsy specimens estimated to be approximately 5%.¹⁶ Clinically, dysplastic nevi differ from common acquired nevi by (1) beginning to appear near puberty instead of in childhood; (2) remaining dynamic throughout adulthood, with an increase or decrease in atypicality; and (3) continuing to develop throughout life, past the fourth decade.

Although the clinical features of dysplastic nevi are fairly typical, the histologic criteria used to diagnose dysplastic nevi are less clear-cut. This confusion resulted in the National Institutes of Health (NIH) Consensus Conference on Diagnosis and Treatment of Early Melanoma defining the histologic criteria as follows: architectural disorder with asymmetry, subepidermal (concentric eosinophilic and/or lamellar) fibroplasia, and lentiginous melanocytic hyperplasia with spindle or epithelioid melanocytes aggregating in nests of variable size and forming bridges between adjacent rete ridges. Melanocytic atypia

may be present to a variable degree. In addition, there may be dermal infiltration with lymphocytes and the "shoulder" phenomenon (intraepidermal melanocytes extending singly or in nests beyond the main dermal component).¹⁵ The NIH Consensus Conference also suggested changing the name from "dysplastic nevus syndrome" to the rather cumbersome "familial atypical mole and melanoma syndrome." This syndrome was defined as (1) the occurrence of malignant melanoma in one or more first- or second-degree relatives; (2) the presence of a large number of melanocytic nevi, often more than 50, some of which are atypical and often variable in size; and (3) melanocytic nevi that demonstrate certain histologic features.¹⁵

The existence of the familial dysplastic nevus syndrome is widely accepted. In the familial melanoma setting, the risk for the development of melanoma has been shown to be increased 184-fold compared with the general population for family members who have dysplastic nevi but no previous history of melanoma. The risk increased to 500-fold for affected family members who have had a previous melanoma.¹⁷

Patients with dysplastic nevi outside of the familial melanoma setting are also thought to have an increased risk for the development of melanoma; however, the rate is much lower than in those persons from a familial melanoma setting.¹ In a case-controlled study by Tucker et al,⁶ 716 consecutive patients with newly diagnosed melanoma were compared with 1014 control patients. One clinically dysplastic nevus was associated with a two-fold risk for the development of melanoma, whereas 10 or more dysplastic nevi conferred a 12-fold increased risk over patients without dysplastic nevi. Bataille et al⁵ compared 426 cutaneous melanoma cases with 416 controls. They found that the presence of 4 or more atypical nevi was associated with a relative risk for the development of melanoma of 14.3, whereas the presence of one atypical nevus conferred a 3-fold risk.

A major problem in identifying prevalence rates and relative risks in sporadic dysplastic nevi is the poor correlation between the clinical phenotype and the histologic criteria used in the diagnosis of dysplastic nevi. Roush et al¹⁸ examined biopsy specimens from 91 clinically dysplastic nevi and found that only 23 of these were classifiable as histologically dysplastic. Conversely, Klein and Barr¹⁹ examined 58 junctional and compound nevi without clinical signs of dysplasia microscopically. One or more histologic features associated with dysplastic nevi were present in 87.8% of the lesions, two or more were present in 69%, and 3 histologic features were found in 29.3%. These results indicate that classic histologic features of dysplastic nevi commonly occur in

benign acquired nevi. Piepkorn et al²⁰ found a prevalence of dysplastic nevi of 53% in Caucasian subjects in Utah when using histologic criteria alone to diagnose dysplastic nevi. These findings underscore the importance of clinicopathologic correlation in making the diagnosis of dysplastic nevi.

Roush and Barnhill²¹ found that the histologic diagnosis of dysplastic nevi was strongly associated with the total number of nevi of any type on the body. They concluded that the total number of nevi (either normal or clinically atypical) is correlated with nuclear and architectural histologic dysplasia on biopsy findings of the most atypical pigmented lesions in these patients.

In summary, dysplastic nevi occur in both familial and sporadic settings. In evaluation of patients with dysplastic nevi, it is important to correlate the histologic findings with the clinical phenotype. The risk for the development of melanoma in patients with dysplastic nevi is most likely related to several factors, including the total number of nevi (both dysplastic and benign) and family history. Dysplastic nevi most likely represent both a "marker" for those patients at an increased risk for development of melanoma and a precursor lesion to melanoma. Therefore prophylactic removal of dysplastic nevi does not eliminate the risk of subsequent melanoma formation. No data are available to assess what effect (if any) such removal has on decreasing the risk for future development of melanoma.

Congenital nevi

Before one can attempt to determine whether congenital nevi represent a precursor to malignant melanoma, a strict definition of congenital nevi must be made. Unfortunately, no unified definition of "congenital nevus" has been adhered to by different authors. The NIH convened a Consensus Conference on "Precursors to Malignant Melanoma" on Oct 24, 1983. Findings of this consensus conference were published in 1984²² and included the statement that "a congenital nevus is a melanocytic nevus that is present at birth." (page 1865) However, the attendees agreed that some lesions first become apparent during infancy; when they do, it is assumed that preexisting nevus cells were present.

This group concluded that the "classic" microscopic description of congenital nevi includes nevus cells in the following locations: (1) the lower two thirds of the dermis, occasionally extending into the subcutis; (2) between collagen bundles distributed as single cells or cells in single file or both; and (3) in the lower two thirds of the reticular dermis or subcutis associated with appendages, nerves, and vessels. However, it was noted that some congenital

nevi do not have these microscopic features. This fact could lead to discrepancies when studies examining the malignant potential of congenital nevi are predicated on case findings by microscopic appearances rather than by clinical data.

Congenital nevi have arbitrarily been divided into groups according to their size in infancy: small (<1.5 cm in diameter), medium (1.5-20 cm in diameter), and large (>20 cm in diameter).²² Large congenital nevi usually do have the classic microscopic findings of congenital nevi, whereas small congenital nevi most often do not show these classic features. Medium-sized congenital nevi may or may not show these classic microscopic features.²²

In 1982, Rhodes and Melski²³ tried to estimate the risk of melanoma associated with small congenital nevi. This work is often cited in review articles because it is one of the few articles that attempts to quantify a risk based on mathematical computations. The authors concluded that there was a 21-fold increase in melanoma risk for persons with small congenital nevi when nevi were ascertained by history and a 3- to 10-fold increase in risk when nevi were ascertained by histology. Unfortunately, several flaws were present in this study. Only 5 of the 20 congenital nevi that were found in association with melanoma by the "clinical history" method were substantiated as being present at birth by direct interview with the parents. Fifteen of the 20 cases were only indirectly documented by previous parental statements to the patient. Walton, Jacobs, and Con²⁴ noted that when historical questionnaires of family members were used, only one third of pigmented lesions in infancy were confirmed to be nevocellular nevi when examined microscopically. A second problem with the Rhodes and Melski study was possible selection bias. Of their 234 melanoma specimens, 8.1% were associated histologically with a nevocellular nevi with congenital features. This association is 8 times higher than data published by Kopf, Barb, and Hennessey.²⁵ Therefore the significance of the conclusions drawn from this study is questionable.

Illig et al²⁶ reviewed 48 "small" congenital melanocytic nevi (<10 cm in diameter by their definition). Only two of these lesions histologically revealed nevus cells in the lower third of the dermis or subcutis. The remaining 46 lesions had nevus cells confined to the upper two thirds of the dermis. All of the melanomas that formed in these patients were of "epidermal" origin, and all formed after 18 years of age. None of these melanomas displayed the neuroectodermal architecture frequently seen in melanoma associated with giant congenital nevi. In fact, the nonepidermal origin of a cutaneous melanoma in small congenital nevi is exceedingly

rare,^{27,28} unlike the frequent occurrence of such lesions in giant congenital nevi.

Swerdlow, English, and Qiao²⁹ followed up 265 patients with congenital nevi. Although 2 of the 33 patients with congenital nevi covering more than 5% of the body surface area died from melanoma, no melanomas were detected in the 232 patients in whom the congenital nevi covered less than 5% of the body surface area. Likewise, Sahin et al³⁰ studied 230 medium-sized congenital melanocytic nevi for an average of 6.7 years (to an average age of 25.5 years). No melanomas appeared in this group, and the authors concluded that their short-term follow-up study did not support the view that there is a clinically significant increased risk for malignant melanoma arising in banal-appearing, medium-sized, congenital melanocytic nevi.

The lifetime risk of malignant transformation in patients with large congenital nevi has been estimated to be between 5% and 20%.²² Egan et al³¹ prospectively followed up 46 patients with large congenital nevi and found that the cumulative 5-year risk for the development of cutaneous melanoma in these patients was 5.7%. Frequently, neoplasms arising in giant congenital nevi have a heterogeneous morphologic appearance, resulting from aberrant migration of primitive neurocrestic cells.³² Approximately 60% of the melanomas that develop in giant congenital nevi develop during the first decade of life, with the highest rate of malignancy during the first 5 years of life.³³ As many as two thirds of melanomas developing in giant congenital melanocytic nevi have nonepidermal origins.³⁴ Thus the "clinical observation" approach for large congenital nevi will fail to detect most malignant transformations in these patients.

From a therapeutic point of view, since almost all melanomas arising in small congenital nevi are of the epidermal variety and the incidence of malignant degeneration is extremely low, prophylactic removal of these small nevi is not essential. Clinical observation will detect malignant changes in these small congenital nevi. If small congenital nevi are to be excised, delaying this procedure until just before puberty would be appropriate because small congenital nevi do not undergo malignant transformation in prepubertal age groups.

Because of the high risk of malignant transformation in giant congenital nevi, prophylactic excision is often recommended. Unfortunately, this is not always feasible in these large nevi because of their size and multiple satellite lesions. Excision down to fascia does not always completely eliminate the risk of malignant melanoma because these neurogenic primordial cells frequently remain in the deeper tissues, particularly in the leptomeninges.³⁵ In contrast

to small congenital nevi, the greatest risk for malignant degeneration in giant congenital nevi exists before the age of 10 years. Therefore, to confer a benefit from prophylactic removal, these procedures should be performed early in life.

In conclusion, it appears that the malignant potential of "congenital nevi" may be more dependent on the histologic pattern of the lesion than the clinical size of the nevus. Small congenital nevi frequently lack melanocytes in the deeper dermis, classically associated with the histologic diagnosis of congenital nevi. The increased risk of melanoma formation in large congenital nevi may be a result of transformation of pleuripotential neuromesenchymal cells residing deep in the dermis.³² The "wait and watch" approach in these lesions is not appropriate because melanomas form deep in the dermis and are fatal before surface changes.

Perhaps the best approach to intermediate-sized congenital nevi would be a preoperative punch or small incisional biopsy to determine the histologic growth pattern of the nevus. If the histologic pattern is that of an acquired nevus (superficial variant of congenital nevi), then it could be assumed that the malignant potential is extremely small, and any malignant transformation would most likely be of the epidermal variety, which would be detectable by clinical observation. If, however, the histologic pattern is that of the deeper dermal tumor, then a significant risk may be present; prophylactic excision at the earliest stage possible would be indicated.

EVALUATION

Staging

The original staging classification for melanoma was very simple, but also very imprecise. Patients were considered to have "stage I" disease if the melanoma was limited to the primary site. "Stage II" disease implied metastases up to the regional lymph node basin, but not beyond. "Stage III" disease implied distant metastases. Because each stage encompassed patients with a wide range of prognoses, this staging system was only of marginal benefit.

Dr Clark, and later Dr Breslow, published the observations that the level of invasion into the dermis or subcutaneous fat of the primary cutaneous melanoma has a direct correlation with disease outcome. Clark's levels are as follows: (1) level I: tumor confined to the epidermis with an intact basal lamina (ie, melanoma in situ), (2) level II: melanoma extending through the basal lamina into the papillary dermis, (3) level III: tumor cells filling and expanding the papillary dermis, (4) level IV: extension into the reticular dermis, and (5) level V: extension to the subcutaneous fat.³⁶ Breslow's microstaging tech-

Table I. The 1988 American Joint Committee on Cancer Staging system⁴⁰

Stage	Criteria*	TNM
IA	Localized melanoma ≤ 0.75 mm or level II	T1N0M0
IB	Localized melanoma 0.76-1.5 mm or level III	T2N0M0
IIA	Localized melanoma 1.5-4 mm or level IV	T3N0M0
IIB	Localized melanoma >4 mm or level V	T4N0M0
III	Nodal metastases involving only one regional lymph node basin or fewer than 5 in-transit metastases in the absence of nodal disease	Any T, N1M0
IV	Advanced regional metastases or distant metastases	Any T, any N, M1 or 2

*When thickness and level of invasion do not coincide within a T classification, thickness takes precedence.

nique utilizes an ocular micrometer to measure the vertical thickness of the melanoma from the granular layer (or base of the ulcer when present) to the deepest portion of the melanoma that is noncontiguous with appendageal structures.³⁷

Breslow depth has subsequently been found to have a stronger prognostic value than the Clark level. However, many dermatopathologists still report the Clark level because it may be prognostically important in select cases.^{38,39} In 1988, the American Joint Committee on Cancer (AJCC) revised the staging system for melanoma to incorporate the Breslow thickness and the Clark level on a "TNM" (ie, T, tumor thickness; N, nodal metastasis; M, distant metastasis) basis.⁴⁰ The original AJCC staging classification is still frequently used and is summarized in Table I.

In 1997, a new staging system was proposed on the basis of a critical analysis of the accuracy of the AJCC staging classification.⁴¹ This analysis was achieved with the use of Kaplan-Meier survival curves from previously published large series to examine the impact on survival of level of invasion, presence of ulceration, local recurrences, satellite metastases, in-transit metastases, and extent of nodal metastasis. The Executive Committee of the AJCC approved this proposal in principle in June 1999, with final recommendations expected in the year 2001.

The following changes were suggested to improve the accuracy of the original AJCC staging classification: (1) Clark's level of invasion was eliminated from the system, since it adds little to prognosis and tends to be less accurate and less reproducible than Breslow depth; (2) tumor thickness stratification cutoffs were changed to 1, 2, and 4 mm since these numbers provided a better prediction of prognosis and were easier to use than the previously used cutoffs of 0.75, 1.5, and 4 mm; (3) since microscopic ulceration was found to be the most statistically significant independent adverse prognostic pathologic feature outside of tumor thickness, it is

incorporated into the classification system by adding an "a" to the T number to indicate no ulceration or a "b" to indicate the presence of ulceration; (4) the presence of microsattelites (histologic) has the same prognostic significance as macrosattelites (those evident clinically) and local recurrence. All are now classified as stage III disease; (5) in-transit or satellite lesions on the head and neck or truncal regions portend a worse prognosis than when present on the extremity, and these cases are upgraded to be stage IIIb; (6) the number of regional lymph nodes involved is a much more powerful predictor of survival than the extent of individual lymph node involvement by physical or pathologic examination.

In conclusion, revision of the staging system for patients with cutaneous melanomas reflects progress in our ability to more accurately stratify patients into prognostic categories. The price for increased accuracy is increased complexity with each revision. Shortcomings of all staging systems include the lack of incorporation of individual characteristics such as anatomic location and gender, both of which have been shown to have independent prognostic significance.⁴²⁻⁴⁴ In addition, important pathologic indicators of biologic behavior such as regression and angiolymphatic invasion should not be ignored when present.⁴⁵ Finally, one should realize that prognostic information obtained from the discussed staging systems may not accurately reflect variants of melanoma, including desmoplastic, neurotropic, mucosal and ocular melanomas.⁴⁶

Laboratory testing

For several years, most patients diagnosed as having malignant melanoma have been subjected to extensive laboratory evaluation, which has included various blood chemistries, chest roentgenograms, and more advanced staging examinations (eg, computed tomographic [CT] scans). Recently, several studies have called into question the need for screening laboratory work in patients who have no systemic signs or symptoms indicative of metastatic

disease. The Melanoma Consensus Conference of 1992, sponsored by the NIH, concluded that staging work-up was not indicated in melanomas 1.00 mm or less in thickness.¹⁵

Weiss et al⁴⁷ studied 261 patients with malignant melanomas thicker than 1.69 mm with or without regional lymph node involvement. Of the 145 patients with recurrent disease, 68% were identified by history alone. Physical examination of patients without symptoms led to the diagnosis of recurrent disease in an additional 26%. Laboratory results were never a sole indicator of recurrent disease. Although either complete blood cell count or liver function tests were abnormal in 11% of the patients, each of these patients had symptoms or physical findings indicative of metastasis before laboratory work was obtained. The authors concluded that routine blood analysis had limited value in postoperative follow-up of patients with resected intermediate- and high-risk melanomas. Jillella, Mani, and Nair⁴⁸ performed a similar study of 279 patients with AJCC stage I-III malignant melanoma. These patients were followed up by history, physical examination, laboratory evaluation, and chest roentgenography. Of the 49 patients who had recurrences, no recurrence was detected by blood studies.

Lactate dehydrogenase (LDH) has been advocated by some as a useful marker for liver metastases. Of the 121 patients with AJCC stage III and IV disease studied by Finck, Giuliano, and Morton,⁴⁹ elevated LDH was the first indicator of recurrent disease in 15 patients (12.5%). However, Buzaid et al⁵⁰ reported low sensitivity of LDH as an indicator for distant metastases. Serum LDH level may indicate distant metastases, particularly of the liver, but its specificity and sensitivity are low. More important, early detection of liver metastases rarely affects long-term survival of patients because liver metastases occur typically in the clinical setting of widespread metastatic disease.⁵¹

Terhune, Swanson, and Johnson⁵² evaluated the use of initial staging chest roentgenography in 876 patients with localized melanoma. Only one (0.1%) had a true-positive chest x-ray demonstrating pulmonary metastasis during the initial work-up. This one true-positive chest x-ray was confirmed after additional work-up of 130 suspect chest x-rays detected on initial examination from these 876 patients. Although a specific cost analysis was not performed, the authors stated "the high false-positive rate of 15% led to costly investigations and contributed to an increase in the patient's anxiety level." (page 572) When melanoma metastasizes to the lungs, it usually appears as multiple small foci. Because the resolution of plain films is usually limited to lesions of 1 cm or

larger, routine chest x-rays have limited capacity to detect these early metastases.⁵²

Weiss et al⁴⁷ also evaluated the usefulness of chest x-rays as follow-up tests for detecting recurrent disease in patients with intermediate- and high-risk melanomas. Of the 145 patients in whom recurrent melanomas developed, only 9 patients (6%) with recurrent disease had abnormal chest x-rays as the only abnormal finding. Although 5 of these patients underwent thoracotomy, only one patient remained disease free over the long term as a result of diagnosing recurrent melanoma by chest x-ray. Jillella, Mani, and Nair⁴⁸ showed that when patients were repeatedly educated regarding signs and symptoms of melanoma recurrence, 94% of those patients with recurrences of their disease detected the recurrences by themselves. In those patients whose original melanoma was node negative, 100% of recurrences were detected by the patients.

Weiss et al⁴⁷ studied the financial burden of chest x-rays during a 5-year follow-up period for 261 patients. By eliminating laboratory studies and chest x-rays in asymptomatic patients, the total cost of following up these 261 patients dropped by 89% from \$421,000 to \$48,000. This estimate did not include money that would have had to be spent on more costly subsequent testing because of false-positive tests of laboratory studies/chest x-rays or follow-up examination costs necessary because of these false tests.

Although randomized prospective studies have not been undertaken with regard to the effect that routine chest radiographs have on survival duration in patients with malignant melanoma, such studies have been performed in patients with primary breast cancer. In the multicenter GIVIO investigators' study,⁵³ 1320 patients with breast cancer were followed up for longer than 5 years. Half of these patients were followed up by history and physical examination as well as annual mammograms. The other half of the study population also underwent additional studies, including bone scans, liver scans, chest x-rays, and blood tests. No significant differences were noted between the two groups with regard to overall survival, time to detection of a recurrence, or health-related quality of life measurements (ie, overall health and quality of life perception, emotional well-being, body image, social functioning, symptoms, and satisfaction with care).

Because of the limited ability of chest radiographs to pick up early metastatic disease, the use of computed tomography has frequently been used in an attempt to diagnose early metastatic disease. In the largest retrospective study to date, Buzaid et al⁵⁴ evaluated the usefulness of CT scans of the chest and

abdomen in detecting occult metastatic disease. Twenty-nine (19%) of the 151 patients had a CT scan that was considered suspect for metastasis. Of these 29 patients, only one patient was found to have regional nodal disease and one additional patient had distal nodal metastases. Staging CT scans failed to detect occult metastases in all 35 patients who subsequently experienced metastases at distant sites and in all 7 patients in whom regional nodal recurrences subsequently developed. Furthermore, 21 patients (17%) had false-positive findings that required further costly work-up. These additional tests (eg, thoracotomies, liver biopsies) added significantly to patient morbidity and anxiety. The authors concluded that CT scans were not useful for detecting occult melanoma metastases in patients with primary melanoma.

Iscoe et al⁵⁵ reviewed 393 patients with stage I malignant melanoma to determine the value of staging investigations. A total of 264 blood tests, 345 chest x-rays, 50 CT scans of the chest, 52 CT scans of the brain, 72 bipedal lymphangiograms, 207 radionuclide liver/spleen scans, and 166 bone scans were performed. The clinical status was changed in only one patient as a result of a positive lymphangiogram.

Several other similar studies have been published failing to document the benefit of advanced screening examinations looking for occult malignancy in otherwise asymptomatic patients. Roth et al,⁵⁶ Thomas et al,⁵⁷ Evans et al,⁵⁸ Au et al,⁵⁹ and Jonsson et al⁶⁰ reported on a total of 520 patients with melanoma with no evidence of metastasis by history or physical examination and found no value to liver, brain, bone, or whole-body scintigraphy because no occult metastases were discovered by these methods. Although these retrospective studies do not address the work-up of patients with high-risk or recurrent disease, the evidence to date does not support the continued use of these tests in the work-up of asymptomatic patients with primary melanoma. The main exception for obtaining these studies on asymptomatic patients would be in those multidisciplinary referral centers conducting ongoing prospective studies. However, even at referral centers such as the University of Michigan Multi-Disciplinary Melanoma Clinic, "serum chemistries, chest radiographs, or computed tomography scans are not routinely ordered for patients with local disease unless there is clinical suspicion."⁶¹

Newer techniques to supplement or eventually replace current laboratory tests are currently in the investigational stage. One of these, positron emission tomography is based on the premise that malignant tumors have a higher metabolic rate than normal tissue and therefore utilize more glucose.^{62,63} The goal of positron emission tomography is to be

able to screen the entire body for occult metastases. Early reports have suggested that metastases may be detectable up to 6 months earlier than by physical examination or conventional imaging.⁶⁴ Routine clinical application is currently limited to only a few investigational centers.

Photography

The best way to reduce mortality from cutaneous melanoma is through early diagnosis, when the tumor is thin. High-risk patients who are being followed up with periodic surveillance have been proven to have significantly thinner and less invasive melanomas compared with patients whose tumors are diagnosed at first encounter.⁶⁵ It has been postulated that small tumors might otherwise be overlooked in the absence of baseline photography.⁶⁶ In general, small-diameter tumors are more likely to be thinner or in situ when compared with larger diameter melanomas.⁶⁷⁻⁶⁹

Total body photography has been advocated by many authors to document stability or instability of nevi in people at high risk for cutaneous melanoma.⁶⁶ The philosophy behind the use of total body photography is that relatively subtle changes in preexisting nevi that might otherwise be overlooked without baseline photography might be detected at an earlier time.^{70,71} In addition, documentation of new nevi would improve with baseline photography. Approximately 41% of respondents in a survey of nonmilitary-accredited Dermatology Residency Programs in the United States use baseline photography in 90% or more of their patients who have dysplastic nevi.⁷² Several techniques for obtaining photographic series in these patients have been described.^{73,74} No standardized technique, however, has been adapted universally.

Several reports have been published touting the benefits of total body photography in the diagnosis of potentially curable cutaneous melanoma. Rivers et al⁷⁵ claimed that 10 of 18 patients being followed up for atypical moles had an early diagnosis of cutaneous melanoma made as a direct result of changes detected on comparison to baseline photography. Similarly, Kelly et al⁷⁶ detected 11 of 20 cutaneous melanomas because of changes in comparison with baseline photographs in 278 adults who were being followed up prospectively. Unfortunately, definitive studies in which high-risk patients are followed up prospectively with and without the use of baseline total body photographs have not been performed to determine whether the use of photography improves long-term survival in high-risk patients.

Advocates of total body photography claim that photographs aid in the detection of new or changing

moles in high-risk patients, which then can be excised. Opponents claim that photographing patients with multiple atypical moles leads to unnecessary surgical removal of many nevi. By definition, patients with dysplastic nevus syndrome continue to develop new lesions throughout life.^{70,71} In addition, dysplastic nevi, by definition, undergo morphologic changes with time. Medicolegally, total body photographs could force physicians to remove *any* changing or new moles in these patients.

Ironically, photography might be most helpful in patients *without* multiple nevi or dysplastic nevi, in whom sporadic melanomas develop. These patients typically do not develop new nevi later in life, so that photographic documentation of new nevi occurring in these patients might truly represent an unusual biologic occurrence that warrants biopsy. Perhaps the most compelling reason to use photography in this patient group is to reassure patients that a nevus which they think is either new or changing is, in fact, stable as determined by photography.

Epiluminescence

Epiluminescence microscopy (ELM), also known as dermatoscopy or skin surface microscopy, is an *in vivo*, noninvasive technique that is often used to enhance visualization of microscopic structures of pigmented lesions. The technique uses a hand-held magnifying instrument, called a "dermatoscope," and uses the optical phenomenon of oil immersion, which eliminates light refraction and makes subsurface structures of the skin more visible to the operator's eye. If ELM is used and interpreted properly, a clinician may benefit by increasing the accuracy of his or her presurgical impression of a suspect pigmented lesion by adding a rough preview of the lesion's microscopic features.^{77,78} In inexperienced hands, ELM has been shown to decrease the clinician's diagnostic accuracy.⁷⁹

ELM is probably most useful in elucidating features of nonmelanocytic lesions that may masquerade as cutaneous melanomas by gross morphology. Two frequently encountered examples are thrombosed eruptive hemangiomas and seborrheic keratoses. ELM would show sharply demarcated red to red-blue lagoons with absence of melanin in typical hemangiomas, whereas seborrheic keratoses may show pseudofollicular openings and horned pseudocysts.⁸⁰ Classic features of a nonmelanocytic lesion as described may reassure the clinician and prevent the patient from undergoing an unnecessary biopsy.

Conversely, the appearance of "typical" melanoma features by ELM should reinforce a clinician's impression that a biopsy is warranted. When used to further evaluate morphologically benign-appearing

melanocytic lesions that are of concern to the patient, ELM features suggestive of melanoma will be present in a minority of cases that may have otherwise been dismissed as benign appearing.

There are two general techniques employed when ELM is used for evaluation of pigmented lesions. Both methods rely on giving a numeric value to atypical features and calculating a score. One is the ABCD method, which is touted as being the simpler method to learn. An extension of the clinical morphologic ABCD criteria, the letters stand for *a*symmetry, *b*order pigment characteristics, *c*olor variation, and *d*ifferential structure.⁷⁸ Dermatologists formally trained with this method can improve their diagnostic accuracy in predicting melanoma up to 80%. The largest drawback of this method is that it requires the use of a cumbersome numbering system.⁸⁰

The second method evaluates individual features identifiable by ELM believed to be predictors of melanoma. In 1989, a consensus meeting held in Hamburg⁸¹ identified the following 6 features as predictors of melanoma: irregular, prominent, and broad pigment network; black dots; radial streaming; irregular brown globules; gray-blue areas; and white, scarlike areas. More recent studies have shown the presence of irregular vascular structures⁸² and the presence of pseudopod formation⁸³ to be additional helpful features in the identification of melanoma. An atypical pigment network, gray-blue areas, and an atypical vascular pattern are the strongest predictors of melanoma and are therefore weighted most heavily and receive a score of "2" with this method. Radial streaming, irregular diffuse pigmentation, irregular dots and globules, and presence of a regression pattern each get a score of "1." A total score of "3" is indicative of melanoma.⁸² This method is much easier and faster to calculate and is more sensitive (but less specific) than the ABCD method.⁸²

Each of the listed features correlates to a microscopic feature found more commonly in melanoma than in benign nevi or other benign pigmented neoplasms⁸² (Table II). Irregular pigment network, black dots, radial streaming, and irregular brown globules are manifestations of architectural disorder of melanocytes. Gray-blue areas correspond to areas of deep reticular dermal invasion by melanocytes. White, scarlike areas represent areas of regression, whereas irregular vascular typology represents angiogenesis. However, there is some overlap between ELM features typical of melanoma and benign neoplasms, just as there is overlap on routine histology.⁸⁰ Severely dysplastic nevi, Spitz nevi, and pigmented spindle cell nevi may all be indistinguishable from melanoma by ELM.⁸⁰

Table II. Epiluminescence microscopy (ELM) criteria and their histologic correlations

ELM	Histologic correlation
Atypical pigment network Gray-blue areas	Hyperpigmented or broad rete ridges with irregular shape or distribution Pigmented melanophages or melanocytes of mid reticular dermis location
Atypical vascular pattern Radial streaming (streaks) and pseudopods Irregular diffuse pigmentation (blotches)	Neovascularization or vascularized nests of amelanotic cells Confluent radial junctional nests of melanocytes Hyperpigmentation throughout all levels of the epidermis or upper dermis (in melanocytes or melanophages)
Irregular dots and globules Regression pattern	Aggregates of pigment of stratum corneum, junctional, or dermis location Areas of loss of pigmentation and fibroplasia, with scattered dermal melanophages

Adapted from Argenziano G, Fabbrocini G, Carli P, DeGiorgi V, Sammarco E, Delfino M. Arch Dermatol 1998;134:1563-70.

ELM has been advocated to help in the detection of early melanomas. However, the ELM feature most common in thin melanomas (defined as having a Breslow thickness of <0.75 mm) is an irregular pigment network. Unfortunately, dysplastic nevi typically display hyperpigmentation and bridging of the rete ridges, which give them a similar appearance by ELM. In a study by Argenziano et al,⁸² melanocytic nevi were more likely to have an irregular pigment network than melanomas (34% vs 23%). However, this feature is still advocated as a “major” ELM criterion for melanomas. Another study⁸⁴ reported that while the presence of abnormal pigment networks in thin melanomas had 95% sensitivity, the specificity was only 32%.

Thicker melanomas (>0.75 mm depth) are more likely to have gray-blue areas or irregular vascular patterns (or both) and often no evidence of an irregular pigment network.⁸⁴ Often, some of the features seen in thin melanomas such as a broad pigment network become obliterated in thicker lesions.

Increased specificity is obtained by the addition of more ELM features. However, sensitivity is naturally compromised with the requirement for greater numbers of features. In addition, spending the time necessary to numerically weigh various features and perform mathematical calculations to improve one’s specificity is not only impractical for a busy clinician, but may in fact be detrimental by decreasing ELM sensitivity.

Dermatologists trained in the use of ELM can improve their diagnostic accuracy of melanoma from about 65% using the unaided eye to approximately 80% with the benefit of ELM.⁷⁸ However, even with ELM, a trained dermatologist can be fooled by the appearance of a melanoma at least 20% of the time. Kittler et al⁸⁵ showed that a patient’s report of change in a lesion is an important risk factor for melanoma. If added into a diagnostic equation along

with morphologic and ELM characteristics, this historical factor significantly improves the diagnostic accuracy of predicting melanoma. Their study underscores the importance of change—a clinical factor that cannot be assessed by a single ELM examination.

Menzies et al⁸⁶ examined 107 patients with biopsy-proven melanoma and found that 9 (8%) of these had no characteristic ELM findings before biopsy. Seven of the “featureless” melanomas were reported to have changed by the patient and the other two were in areas that the patients could not see. In addition, two thirds were pigmented, but were evaluated as having a regular pigment network without broad ridges or other ELM characteristics of melanoma. The remaining one third were hypopigmented and also lacked ELM characteristic features of melanoma.

More than 90% of melanomas are of the “superficial spreading” and “nodular” histologic types. The literature is relatively devoid of ELM data of less usual melanoma variants such as amelanotic melanomas, desmoplastic melanomas, lentigo maligna melanoma, or nevoid melanoma. Because these histologic subtypes often have different histologic features from superficial spreading and nodular subtypes, they are also more likely to lack defined ELM features for melanoma.

In summary, ELM is a quick and noninvasive procedure that may enhance the clinician’s ability to diagnose a pigmented lesion as a melanoma or provide satisfactory evidence of a benign process such as a seborrheic keratosis or a vascular neoplasm in morphologically difficult cases. Extreme caution should be used with the technique, however, because even experienced users may obtain a false sense of security in 20% or more cases of melanoma that lack classic ELM features of melanoma. In inexperienced hands, ELM actually decreases diagnostic accuracy.⁷⁹ This technique should not be used without formal training. An interactive 9-hour course over 3 days with

knowledgeable and experienced instructors has been reported to be adequate for ELM training purposes.⁸⁷ The decision to perform a biopsy of a lesion of moderate to high clinical suspicion for melanoma before ELM observation should not be changed by the lack of ELM criteria for melanoma.

THERAPY

Surgical margins

The primary surgical goal in the treatment of melanoma is to excise the tumor to achieve histologically free margins with low likelihood of local recurrence or persistent disease. Complete excision results in an 8-year survival rate of more than 95% for thin (<1 mm), invasive melanomas and essentially cures melanoma *in situ*.^{88,89} A large survey of practicing dermatologists conducted by the New York University Melanoma Group found marked variability in surgical margins being used to remove melanomas of varying depths.⁹⁰ Up until a few decades ago, 5-cm excisional margins were the standard of care for all melanomas. These recommendations had been handed down from generation to generation based on the recommendation by Handley⁹¹ in 1907 based on autopsy findings in a single case of metastatic disease. Current recommendations are still largely arbitrary, although 3 well-conducted prospective studies have been performed to provide insight on appropriate surgical margins.

A prospective, randomized study conducted by the World Health Organization (WHO) demonstrated that melanomas up to 2 mm in depth can safely be excised with a 1-cm margin with no detrimental effect on patient survival.^{92,93} In this study, narrow excision (1-cm margins) was performed on 305 patients, whereas wide excision (≥ 3 cm) was performed on 307 patients. The subsequent development of local recurrences or metastatic disease (either regional nodes or distant organs) was not statistically different between the two groups. Disease-free survival rates and overall survival rates were also similar in the two groups. Four local recurrences developed in patients with lesions 1.1 to 2.0 mm in thickness, all in the 1-cm margin excision group. No local recurrences developed in the patients in the 3-cm margin group. This difference was not statistically significant. On the basis of these 4 local recurrences, several authors have misinterpreted the results of this study and have concluded that only melanomas up to 1 mm in thickness should be excised with 1-cm margins.

There is no evidence that patient survival is adversely affected if local recurrence results from inadequate excision of the primary melanoma (ie, persistent disease), providing the residual *in situ* or

radial growth-based tumor is promptly reexcised.⁸⁹ What has been shown clearly is that patients with metastatic disease or recurrence in regional lymph nodes have a median survival that is significantly shorter than patients experiencing local recurrence.⁹⁴ Ironically, what has been ignored in several reviews of the classic WHO study is that patients who received wide excision (3 cm) actually had a higher incidence of regional nodal metastasis than those who received narrow excisions (1 cm). In fact, the number of patients with disseminated disease (in-transit metastasis, regional nodal metastasis, or distant metastasis) was identical in both narrow and wide excision groups. In summary, this prospective, randomized study by the WHO demonstrates that melanomas up to 2 mm (not 1 mm) in depth can be excised with a 1-cm margin without compromising patient survival.

Another multi-institutional, randomized surgical trial looked at the efficacy of 2-cm surgical margins compared with 4-cm surgical margins in the treatment of intermediate-thickness melanomas (1-4 mm).⁹⁵ Although this study confirmed progressive increases in local recurrence rates with tumors of increasing thickness, local recurrences (defined as recurrence within 2 cm of the primary melanoma scar) were actually twice as common after a 4-cm excision than they were after a 2-cm excision (not statistically significant). This fact is in direct conflict with the dogma that wider excisions lead to a reduction in local recurrences.

Although most studies have looked at recurrence rates of melanoma based on depth of the tumor (Breslow measurement), a study by Zitelli, Braun, and Hanusa⁹⁶ found that the diameter of cutaneous melanomas is also an important factor in assigning surgical margins. The authors prospectively reviewed the surgical margins necessary to excise 553 primary cutaneous melanomas using Mohs micrographic surgical techniques. Overall, 83% of melanomas were successfully excised with a 6-mm margin, 95% of melanomas were removed with a 9-mm margin, and a 1.2-cm margin was necessary to remove 97% of the melanomas. Margins to remove melanomas on the head, neck, hands and feet were wider than those necessary on the trunk and extremities. In addition, melanomas with diameters larger than 2 to 3 cm required wider margins than those for smaller melanomas.

Using data from this prospective study, the authors determined appropriate surgical margins necessary for adequate excision of melanomas by standard surgical techniques. They concluded that 1-cm margins were appropriate for melanomas on the trunk and proximal extremities that were smaller than 2 cm in

Table III. Surgical margins for excision of primary cutaneous melanoma based on clinical and histologic criteria

Clinical presentation of melanoma	Breslow depth	
	<2.0 mm	2.0-4.0 mm
Trunk, proximal extremities, <2.0 cm diameter	1.0 cm	2.0 cm
Trunk, proximal extremities, >2.0 cm diameter	1.5 cm	2.0 cm
Head, neck, hands, feet, <3.0 cm diameter	1.5 cm	2.0 cm
Head, neck, hands, feet, >3.0 cm diameter	2.5 cm	2.5 cm

diameter, whereas 1.5-cm margins were appropriate for tumors greater than 2 cm in diameter. For melanomas on the head, neck, hands, and feet, a minimum surgical margin of 1.5 cm was recommended, and a margin of 2.5 cm was recommended for melanomas with diameters larger than 3 cm.

A summary of adequate surgical margins based on these 3 prospective controlled studies is presented in Table III. No scientific data are available with regard to surgical margins for melanomas thicker than 4 mm.

It is often recommended that excision of melanoma should extend to the muscular fascia. This recommendation has been based on “the anatomic understanding that the lymphatics drain to the regional lymph nodes in the subcutaneous tissue extending to the underlying muscle fascia.”⁹⁷ (page 533) Unfortunately, this flawed premise presumes the presence of an anatomic filter in the lymphatic system directly beneath the tumor where in-transit melanoma cells could somehow be arrested on their journey to the regional lymph nodes. In fact, lymphoscintigraphy and sentinel node studies are possible because of the uninterrupted drainage from the skin to the regional nodal basin despite previous melanoma excision. Excision of small portions of the lymphatic channel system beneath the primary tumor in an attempt to prevent regional metastasis makes no anatomic or physiologic sense. No controlled prospective studies have examined primary melanoma excision to the depth of the deep subcutaneous fat versus excision to the underlying fascia. However, surgical principles dictate excision into the subcutaneous fat for appropriate undermining and wound closure.

Elective lymph node dissection

The vast majority of patients presenting with melanomas of Breslow thickness of up to 1.0 mm have an excellent prognosis with simple conservative re-excision around the primary site alone.^{41,42} Therefore only the most aggressive clinicians have attempted to justify the morbidity associated with

elective lymph node dissection (ELND) for patients presenting with low-risk disease, and currently this practice is generally considered unacceptable. However, some physicians have recommended regional ELND for all patients presenting with intermediate-risk (Breslow depth, 1.0-4.0 mm) and high-risk (Breslow depth, >4.0 mm) melanomas based primarily on observations and extrapolation.

The status of metastases in regional lymph nodes among patients with melanoma has a predictive value for survival. If lymph node metastases are present, the 5-year survival rate of patients decreases by approximately 30% to 50%.⁴¹ Approximately 20% of all patients with intermediate- and high-risk cutaneous melanomas with no evidence of clinical, radiologic, or laboratory evidence of metastatic disease harbor pathologically evident disease in the regional lymph node basin at the time of presentation.^{45,98-100} On the basis of the theory that melanoma tends to metastasize in an orderly fashion and most often involves the regional lymph node basin before distant sites, proponents of ELND contend that removing regional lymph nodes in all patients with intermediate- and high-risk melanomas would benefit the subset with microscopic metastases. The intervention would theoretically prevent the subsequent sequence of likely metastatic events and may therefore improve overall survival of the patient. Opponents to ELND argue that removing regional lymph nodes has not been shown to prevent metastases to distant sites, and excision of microscopic metastases might actually impair the body's own immune system in its attempt to produce antibodies against residual tumor cells.¹⁰¹

Four large prospective trials have addressed the issue of whether or not ELND affects survival of patients with cutaneous melanoma clinically confined to the skin.¹⁰²⁻¹⁰⁵ All 4 studies showed no difference in long-term survival between those patients who underwent regional lymph node dissection in addition to wide re-excision and those who had wide re-excision alone. However, subgroup analysis of the Intergroup Melanoma Surgical Program study¹⁰⁵

showed a statistically significant improvement in survival among those patients younger than 60 years with melanomas 1 to 2 mm thick who underwent ELND as compared with those who did not. However, the inherent dangers of retrospectively reanalyzing subgroups of patients from larger studies should make one interpret these data cautiously.

Patients with clinically involved regional lymph nodes and no evidence of distant metastases are believed to gain a survival benefit from a therapeutic lymph node dissection as evidenced by the indirect evidence of staging survival curves.⁴¹ However, this has never been substantiated by prospective studies. Likewise, no direct data are available regarding the survival benefit from ELND on patients with microscopic nodal disease.

Sentinel lymph node dissection

When performed electively in all patients with intermediate (1-4 mm) to thick (>4 mm) melanomas, ELND produces significant morbidity without any known benefit for the 80% of patients with no lymph node involvement. Addressing this problem, the sentinel lymph node dissection (SLND) technique has recently been advocated for use in patients with melanoma. The procedure was first described by Morton et al¹⁰⁶ in 1992 for use in patients with cutaneous melanoma. When properly performed, the procedure provides accurate information regarding a patient's subclinical lymph node status with minimal morbidity.¹⁰⁶⁻¹¹⁰

The procedure has been described in detail^{106,110,111} and simplistically entails the intradermal injection of a radiolabeled substance such as technetium sulfur colloid, usually in combination with a biologic blue dye, into the skin immediately surrounding the site of the primary melanoma. The agents are then taken up by the cutaneous lymphatic channels and "drain" to the regional lymph node bed. Lymphoscintigraphy is utilized to identify the lymph node bed or beds that contain one or more sentinel lymph nodes. A hand-held gamma probe is used during the procedure to detect the immediate site within the targeted lymph node basin where the sentinel lymph node lies. The radioactive substance and blue dye concentrate in the sentinel lymph node(s) before draining to other lymph nodes in the regional basin.¹⁰⁶ An incision measuring approximately 1 cm is made over the locus where the gamma count is high and the sentinel lymph node may be visually confirmed by its color as it also takes up the blue dye.

A two-procedure process is generally preferred for performing SLND. The primary melanoma is narrowly excised in the first step to ensure that the melanoma is of adequate depth (and risk of metasta-

sis) to justify this procedure, which is associated with low morbidity, but is costly. Margins of more than 1 cm or procedures such as flaps or grafts done before lymphatic mapping may disrupt the regional lymphatic flow and impair the ability of the surgeon to correctly identify the sentinel lymph node(s). This is especially true for cutaneous melanomas on the head, neck, trunk, or proximal extremities.¹¹² The second procedure involves the SLND followed by re-excision of the primary site with appropriate margins.

The SLND provides accurate information only if performed under ideal circumstances by a surgeon adequately trained in the procedure because surgeons with less experience with the procedure have proven to be less successful at correctly identifying the sentinel lymph node(s).¹⁰⁶ When SLND is performed by a surgeon experienced in the method, studies have shown that if the procedure shows no evidence of metastasis, the remaining lymph nodes in the regional lymph node basin will likewise be uninvolved with metastases in more than 98% of the cases.^{107,108}

Presently, the most substantiated use of SLND in melanomas is for obtaining prognostic information.¹¹³ Results of the procedure might help determine whether or not to use adjuvant treatment such as interferon alfa-2b (IFN- α 2b). The Eastern Cooperative Oncology Group (ECOG) Trial EST 1684¹¹⁴ showed a statistically significant disease-free and overall survival among those patients with AJCC stage III melanoma with clinically palpable regional lymph nodes who were treated with IFN- α 2b as compared with those simply observed after surgery. However, subgroup analysis revealed that patients with clinically negative (nonpalpable) but histologically positive nodes did *not* benefit from IFN- α 2b treatment. Thus the very patients identified by SLND are those patients not likely to benefit from IFN- α 2b therapy.

Furthermore, a more recent ECOG trial (E1690)¹¹⁵ raises questions regarding the reproducibility of the beneficial effects of IFN- α 2b for patients with AJCC stage III melanoma. The overall survival difference between patients with stage III disease treated with IFN- α 2b plus complete lymph node dissection of the affected basin versus those treated with complete lymph node dissection alone was not appreciated in this study as it was with ECOG Trial EST 1684. Proponents of the use of IFN- α 2b argue that the lack of difference in overall survival is because many of the patients with no original adjuvant treatment and clinical recurrence of melanoma received IFN- α 2b as salvage therapy after clinical recurrences. IFN- α 2b remains approved by the Food and Drug Administration for AJCC stages IIb and III melanoma (though no statistically signifi-

cant benefit has been shown in any randomized prospective study for stage IIb melanoma at the present time).

In summary, although the technique of SLND is a potentially exciting advancement in the evaluation and treatment of melanoma, the procedure is difficult and expensive and should be performed only by those who perform the procedure on a regular basis. The therapeutic implications of SLND are unproved and await further follow-up data from multi-institutional series. At present, the most appealing use for SLND is as a staging procedure to determine which patients might benefit from further adjuvant therapy. However, effectiveness of adjuvant treatments in patients with clinically occult sentinel node metastases remains unproved. In addition, if the patient is not a potential candidate for interferon therapy (which itself has significant morbidity) for medical, financial, or personal reasons, then SLND procedures are useful only for prognostic information.

CONCLUSION

We have attempted to present an evidence-based summary of the current literature with regard to primary cutaneous melanoma, its diagnosis, precursor lesions, and therapy. Many of the recent advances published regarding melanoma require confirmation. The roles of laboratory testing, photography, and newer diagnostic tools such as ELM to evaluate patients for melanoma or precursor lesions have been presented. These tools can be used as adjuncts in diagnosis and staging melanoma in the hands of experienced practitioners, but do not replace traditional surgical therapy and clinical follow-up. Despite the excitement in the current literature with regard to new interventions such as SLND procedures, their value outside of the clinical trial setting is mainly as a staging procedure until the therapeutic and prognostic utility is substantiated by ongoing prospective randomized studies.

Patients with advanced melanoma are best treated by a multidisciplinary approach, usually at a referral center by those with expertise in the treatment of melanoma. In addition, advancement of melanoma treatment depends on randomized, prospective studies available predominantly at these larger institutions. However, not all patients have access to such referral centers or are appropriate candidates for clinical trials. Patients with localized disease can be treated by practitioners comfortable with this disease, guided by current scientific data.

REFERENCES

1. Rhodes AR, Weinstock MA, Fitzpatrick TB, Mihm MC, Sober AJ. Risk factors for cutaneous melanoma. *JAMA* 1987;258:3146-54.
2. Williams ML, Pennella R. Melanoma, melanocyte nevi and other melanoma risk factors in children. *J Pediatr* 1994;124:833-45.
3. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melanocytic nevi as a major risk factor for malignant melanoma. *J Am Acad Dermatol* 1987;17:459-68.
4. Swerdlow AJ, English J, MacKie RM. Benign melanocyte nevi as a risk factor for malignant melanoma. *BMJ* 1986;292:1555-9.
5. Bataille V, Bishop JA, Sasieni P, Swerdlow AJ, Pinney E, Griffith SK, et al. Risks of cutaneous melanoma in relation to the numbers, types, and sites of naevi: a case-control study. *Br J Cancer* 1996;73:1605-11.
6. Tucker MA, Halpern A, Holly EA, Hartge P, Elder DE, Sagiebiel RW, et al. Clinically recognized dysplastic nevi: a central risk factor for cutaneous melanoma. *JAMA* 1997;277:1439-44.
7. Gallagher RP, McLean DJ, Yang CP, Coldman AJ, Silver HKB, Spinelli JJ, et al. Anatomic distribution of acquired melanocyte nevi in white children. *Arch Dermatol* 1990;126:466-71.
8. Weiss J, Bertz J, Jing EG. Malignant melanoma in southern Germany: different predictive value of risk factors for melanoma subtypes. *Dermatologica* 1991;183:109-13.
9. Grob H, Gouvernet J, Aymar D, Mostaque A, Romano MH, Collet M, et al. Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. *Cancer* 1990;66:387-95.
10. Roush GC, Nordlund JJ, Forget B, Graber SB, Kirkwood JM. Independence of dysplastic nevi from total nevi in determining risk for nonfamilial melanoma. *Prev Med* 1988;17:273-9.
11. Elder DE, Greene MH, Bond EE, Clark WH. Acquired melanocytic nevi and melanoma: the dysplastic nevis syndrome. In: Ackerman AB, editor. *Pathology of malignant melanoma*. New York: Masson; 1981. p. 185-215.
12. Gruber SB, Barnhill RL, Stenn KS, Roush GC. Nevomelanocytic proliferations in association with cutaneous malignant melanoma: a multivariate analysis. *J Am Acad Dermatol* 1989;21:733-80.
13. Clark WH Jr, Reimer RP, Greene M, Ainsworth AM, Mastrangelo MJ. Origin of familial malignant melanomas from heritable melanocytic lesions: the B-K mole syndrome. *Arch Dermatol* 1978;114:732-8.
14. Greene MH, Clark WH Jr, Tucker MA, Elder DE, Kreamer KH, Fraser MC, et al. Precursor naevi in cutaneous malignant melanoma: a proposed nomenclature. *Lancet* 1980;2:1024.
15. Consensus Development Panel on Early Melanoma. Diagnosis and treatment of early melanoma. *JAMA* 1992;268:1314-9.
16. Crutcher WA, Sagebiel RW. Prevalence of dysplastic nevi in a community practice. *Lancet* 1984;1:729.
17. Greene MH, Clark WH Jr, Tucker MA, Kraemer KH, Elder DE, Fraser MC. The prospective diagnosis of malignant melanoma in a population at high risk: hereditary melanoma and the dysplastic nevus syndrome. *Ann Intern Med* 1985;102:458-65.
18. Roush GC, Dubin N, Barnhill RL. Prediction of historical melanocytic dysplasia from clinical observation. *J Am Acad Dermatol* 1993;4:555-62.
19. Klein LJ, Barr RJ. Histologic atypia in clinically benign nevi. *J Am Acad Dermatol* 1990;22:278-82.
20. Piepkorn M, Meyer LJ, Goldgar D, Seuchter SA, Cannon-Albright LA, Skolnick MH, et al. The dysplastic melanoma nevus: a prevalent lesion that correlates poorly with clinical phenotype. *J Am Acad Dermatol* 1989;20:407-15.
21. Roush GC, Barnhill RL. Correlation of clinical pigmentary characteristics with histopathologically-confirmed dysplastic nevi in nonfamilial melanoma patients: studies of melanocytic nevi IX. *Br J Cancer* 1991;64:943-7.
22. Consensus Conference. Precursors to malignant melanoma. *JAMA* 1984;251:1864-6.

23. Rhodes AR, Melski JW. Small congenital nevocellular nevi and the risk of cutaneous melanoma. *J Pediatr* 1982;100:219-24.
24. Walton RG, Jacobs AH, Con AJ. Pigmented lesions in newborn infants. *Br J Dermatol* 1976;95:389-96.
25. Kopf AW, Barb RS, Hennessey P. Congenital nevocytic nevi in malignant melanoma. *J Am Acad Dermatol* 1979;1:123.
26. Illig L, Waidner F, Hundeiker M, Gartmann H, Biess B, Leyh F, et al. Congenital nevi ≤ 10 cm as precursors to melanoma. *Arch Dermatol* 1985;121:1247-81.
27. Sharpe RJ, Salasche SJ, Barnhill RL, Sober AJ. Non-epidermal origin of cutaneous melanoma in a small congenital nevus. *Arch Dermatol* 1990;126:1559-61.
28. Paull WH, Polley D, Fitzpatrick JE. Malignant melanoma arising intradermally in a small congenital nevus of an adult. *J Dermatol Surg Oncol* 1986;12:1176-8.
29. Swerdlow AJ, English JSC, Qiao Z. The risk of melanoma in patients with congenital nevi: a cohort study. *J Am Acad Dermatol* 1995;32:595-9.
30. Sahin S, Levine L, Kopf AW, Rao BK, Traiola M, Koenig K, et al. Risk of melanoma in medium-sized congenital melanocytic nevi: a follow-up study. *J Am Acad Dermatol* 1998;39:428-33.
31. Egan CL, Oliveria SA, Elenitsas R, Hanson J, Halpern AC. Cutaneous melanoma risk and phenotype changes in large congenital nevi: a follow-up study of 46 patients. *J Am Acad Dermatol* 1998;39:923-32.
32. Jerdan MS, Cohen BA, Smith RRL, Hood AF. Neuroextradermal neoplasms arising in congenital nevi. *Am J Dermatopathol* 1985;7(Suppl):41-8.
33. Kaplan EN. The risk of malignancy in large congenital nevi. *Plast Reconstr Surg* 1974;53:421-8.
34. Rhodes AR, Wood WC, Sober AJ, Mihm MC. Non-epidermal origin of malignant melanoma associated with a giant congenital nevocellular nevus. *Plast Reconstr Surg* 1981;67:782-90.
35. Ruiz-Maldonado R, Orozco-Covarrubias ML. Malignant melanoma in children: a review. *Arch Dermatol* 1997;133:363-71.
36. Clark WH Jr, From L, Bernardino EA, Mihm MC Jr. The histogenesis and biologic behavior of primary human malignant melanoma of the skin. *Cancer Res* 1969;29:705.
37. Breslow A. Prognostic factors in the treatment of cutaneous melanoma. *J Cutan Pathol* 1979;6:208.
38. Kelly JW, Sagebiel RW, Clyman S, Blois MS. Thin level IV malignant melanoma: a subset in which level is the major prognostic indicator. *Ann Surg* 1985;202:98-103.
39. Morton D, Davtyan D, Wanek L, Foshay LJ, Cochran AJ. Multivariate analysis of the relationship between survival and the microstage of primary melanoma by Clark level and Breslow thickness. *Cancer* 1993;71:3737-43.
40. Beahrs OH, Meyers MH, editors. American Joint Committee on Cancer: manual for cancer staging. 3rd ed. Philadelphia: Lippincott; 1988. p. 143-4.
41. Buzaid AC, Ross MI, Balch CM, Soong S, McCarthy WH, Benjamin RS, et al. Critical analysis of the current American Joint Committee on Cancer staging system for cutaneous melanoma and proposal of a new staging system. *J Clin Oncol* 1997;15:1039-51.
42. Schuchter L, Schultz DJ, Synnestvedt M, Trock BJ, Guerry D, Elder DE, et al. A prognostic model for predicting 10-year survival in patients with primary melanoma. *Ann Intern Med* 1996;125:369-75.
43. Blois MS, Sagebiel TW, Abarbanel RM, Caldwell TM, Tuttle MS. Malignant melanoma of the skin: the association of tumor depth and type, and patient sex, age, and site with survival. *Cancer* 1983;52:1330-41.
44. Halpern AC, Schuchter LM. Prognostic models in melanoma. *Semin Oncol* 1997;24(Suppl):S4-2-S4-7.
45. Mraz-Gernhard S, Sagebiel RW, Kashani-Sabet M, Miller JR, Leong SPL. Prediction of sentinel lymph node micrometastasis by histological features in primary cutaneous malignant melanoma. *Arch Dermatol* 1998;134:983-7.
46. Sagebiel RW. The pathology of melanoma as a basis for prognostic models: the UCSF experience. *Pigment Cell Res* 1994;7:101-10.
47. Weiss M, Loprinzi CL, Creagan ET, Dalton RJ, Novotny P, O'Fallon JR. Utility of follow-up tests for detecting recurrent disease in patients with malignant melanoma. *JAMA* 1995;274:1703-5.
48. Jillella A, Mani S, Nair B. The role for close follow-up of melanoma patients with AJCC stages I-III: a preliminary analysis. *Proc Am Soc Clin Oncol* 1995;14:413.
49. Finck SJ, Giuliano AE, Morton DL. LDH and melanoma. *Cancer* 1983;51:840-3.
50. Buzaid AC, Tinoco L, Ross MI, Lagha SS, Benjamin RS. Role of computed tomography in the staging of patients with local-regional metastases of melanoma. *J Clin Oncol* 1995;13:2104-8.
51. Balch CM, Houghton AN. Diagnosis of metastatic melanoma at distant sites. In: Balch CM, Houghton AN, Milton GW, et al, editors. *Cutaneous melanoma*. 2nd ed. Philadelphia: Lippincott; 1992. p. 439-67.
52. Terhune MH, Swanson N, Johnson TM. Use of chest radiographs in the initial evaluation of patients with localized melanoma. *Arch Dermatol* 1998;134:569-72.
53. The GIVIO Investigation. Impact of follow-up teaching on survival and health-related quality of life in breast cancer patients: a multicenter randomized controlled trial. *JAMA* 1994;271:1587-92.
54. Buzaid AC, Sandler AB, Mani S, Curtis AM, Poo WJ, Bolognia JL, et al. Role of computed tomography in the staging of primary melanoma. *J Clin Oncol* 1993;11:638-43.
55. Iscoe N, Kersey P, Gapski J, Osoba D, From IL, DeBoer G, et al. Pediatrics value of staging: investigations in patients with clinical stage I malignant melanoma. *Plast Reconstr Surg* 1987;80:233-7.
56. Roth JA, Eiber FR, Bennett LR, Morton DL. Radionuclide photoscanning: usefulness in preoperative evaluation of melanoma patients. *Arch Surg* 1975;110:1211-2.
57. Thomas JH, Panoussopoulos D, Liesmann GE, Jewel WR, Preston DF. Scintiscans in the evaluation of patients with malignant melanomas. *Surg Gynecol Obstet* 1979;149:574-6.
58. Evans RA, Bland KI, McMurtrey MJ, Ballantyne AJ. Radionuclide scans not indicated for clinical stage I melanoma. *Surg Gynecol Obstet* 1980;150:532-4.
59. Au FC, Maier WP, Malmud LS, Goldman LI, Clark WH Jr. Preoperative nuclear scans in patients with melanoma. *Cancer* 1984;53:2095-7.
60. Jonsson PE, Hafstrom L, Hugander A, Cederquist E. Value of liver scintigraphy in pretreatment staging and in follow-up of patients with malignant melanoma. *J Surg Oncol* 1985;29:22-5.
61. Fader DJ, Wise CG, Normolle DP, Johnson TM. The multidisciplinary melanoma clinic: a cost outcomes analysis of specialty care. *J Am Acad Dermatol* 1998;38:742-51.
62. Boni R, Huch-Boni RA, Steinert H, von Schulthess GK, Burg G. Early detection of melanoma metastasis using fludeoxyglucose F 18 positron emission tomography. *Arch Dermatol* 1996;132:875-6.
63. Paquet P, Hustinx R, Rigo P, Pierard GE. Malignant melanoma staging using whole body positron emission tomography. *Melanoma Res* 1998;8:59-62.
64. Damian DL. Positron emission tomography in the detection and management of metastatic melanoma. *Melanoma Res* 1996;6:325-9.
65. Richert SM, D'Amico F, Rhodes AR. Cutaneous melanoma:

- patient surveillance and tumor progression [abstract]. *J Invest Dermatol* 1997;108:36.
66. Rhodes AR. Intervention strategy to prevent lethal cutaneous melanoma: use of dermatologic photography to aid surveillance of high-risk persons. *J Am Acad Dermatol* 1998;39:262-7.
 67. Carli P, Borgognoni L, Reali UM, Giannotti B. Clinicopathological features of small diameter malignant melanoma. *Eur J Dermatol* 1994;4:440-2.
 68. Shaw HM, McCarthy WH. Small-diameter malignant melanoma: a common diagnosis in New South Wales, Australia. *J Am Acad Dermatol* 1992;27:679-82.
 69. Kopf AW, Rodriguez-Sains RS, Rigel DS, Friedman RJ, Bart RS, Grier WRN, et al. "Small" melanomas: relation of prognostic variables to diameter of primary superficial spreading melanomas. *J Dermatol Surg Oncol* 1982;8:765-70.
 70. Barnes LM, Nordlund JJ. The natural history of dysplastic nevi: a case history illustrating their evolution. *Arch Dermatol* 1987;123:1059-61.
 71. Halpern AC, Guerry D IV, Elder DE, Trock B, Synnestvedt M, Humphreys T. Natural history of dysplastic nevi. *J Am Acad Dermatol* 1993;29:51-7.
 72. Shriner DL, Wagner RF. Photographic utilization in dermatology clinics in the United States: a survey of university-based dermatology residency programs. *J Am Acad Dermatol* 1992;27:565-7.
 73. Slue W, Kopf AW, Rivers JK. Total-body photographs of dysplastic nevi. *Arch Dermatol* 1988;124:1239-43.
 74. Shriner DL, Wagner RF, Glowczwski JR. Photography for the early diagnosis of malignant melanoma in patients with atypical moles. *Cutis* 1992;50:358-62.
 75. Rivers JK, Kopf AW, Vinokur AF, Rigel DS, Friedman RJ, Heilman ER, et al. Clinical characteristics of malignant melanomas developing in persons with dysplastic nevi. *Cancer* 1990;65:1232-6.
 76. Kelly JW, Yeatman JM, Regalia C, Mason G, Henham AP. A high incidence of melanoma found in patients with multiple dysplastic naevi by photographic surveillance. *Med J Aust* 1997;167:191-4.
 77. Binder M, Kittler H, Steiner A, Dawid M, Pehamberger H, Wolff K. Reevaluation of the ABCD rule for epiluminescence microscopy. *J Am Acad Dermatol* 1999;40:171-6.
 78. Nachbar F, Stolz W, Merkel T, Cognetta AB, Vogt T, Landthaler M, et al. The ABCD rule of dermatoscopy: high prospective value in the diagnosis of doubtful melanocytic skin lesions. *J Am Acad Dermatol* 1994;30:551-9.
 79. Binder M, Poespoeck-Schwarz M, Steiner A, Kittler H, Muellner M, Pehamberger H, et al. Epiluminescence microscopy of small pigmented skin lesions: short-term formal training improves diagnostic performance of dermatologists. *J Am Acad Dermatol* 1997;36:197-202.
 80. Differential diagnosis of pigmented skin lesions. In: Stolz W, Braun-Falco O, Bilek P, Landthaler M, Cognetta A, editors. *Color atlas of dermatoscopy*. Cambridge: Blackwell Science; 1994. p. 37-51.
 81. Bahmer FA, Fritsch P, Kreuzsch J, Pehamberger H, Rohrer C, Schindera I, et al. Terminology in surface microscopy. *J Am Acad Dermatol* 1990;23:1159-62.
 82. Argenziano G, Fabbrocini G, Carli P, DeGiorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions: comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Arch Dermatol* 1998;134:1563-70.
 83. Menzies SW, Crotty KA, McCarthy WH. The morphologic criteria of the pseudopod in surface microscopy. *Arch Dermatol* 1995;131:436-40.
 84. Argenziano G, Fabbrocini G, Carli P, DeGiorgi V, Delfino M. Epiluminescence microscopy: criteria of cutaneous melanoma progression. *J Am Acad Dermatol* 1997;37:68-74.
 85. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Morphologic changes of pigmented skin lesions: a useful extension of the ABCD rule for dermatoscopy. *J Am Acad Dermatol* 1999;40:558-62.
 86. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. *Arch Dermatol* 1996;132:1178-82.
 87. Grant-Kels JM, Bason ET, Grin CM. The misdiagnosis of malignant melanoma. *J Am Acad Dermatol* 1999;40:539-48.
 88. US Dept of Health and Human Services, Public Health Service. NIH Consensus Development Panel on Early Melanoma: diagnosis and treatment of early melanoma. *JAMA* 1992;268:1314-9.
 89. Swetter SM, Smoller BR, Bauer EA. Cutaneous cancer and malignant melanoma. In: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE, editors. *Clinical oncology*. New York: Churchill-Livingstone; 1995. p. 1023-46.
 90. Salopek TG, Slade JM, Marghoob AA, Rigel DS, Kopf AW, Bart RS, et al. Management of cutaneous malignant melanoma by dermatologists of the American Academy of Dermatology. II. Definitive surgery for malignant melanoma. *J Am Acad Dermatol* 1995;33:451-61.
 91. Handley WS. The pathology of melanocytic growth in relation to their operative treatment, lecture 1. *Lancet* 1907;1:927-33, 996-1003.
 92. Veronesi U, Cascinelli N, Adams J, Balch C, Bandiera D, Barchuk A, et al. Thin stage I primary cutaneous malignant melanoma: comparison of excision with margins of 1 or 3 cm. *N Engl J Med* 1988;318:1159-62.
 93. Veronesi U, Cascinelli N. Narrow excision (1 cm margins): a safe procedure for thin cutaneous melanoma. *Arch Surg* 1991;126:438-41.
 94. Reintgen DS, Vollmer R, Tso CY, Seigler HF. Prognosis for recurrent stage I malignant melanoma. *Arch Surg* 1987;122:1338-42.
 95. Balch CM, Urist MM, Karakousis CP, Smith TJ, Temple WJ, Drzewiecki K, et al. Efficacy of 2 cm surgical margins for intermediate-thickness melanomas (1-4 mm): results of a multiinstitutional randomized surgical trial. *Ann Surg* 1993;218:262-7.
 96. Zitelli JA, Braun CD, Hanusa BH. Surgical margins for excision of primary cutaneous melanomas. *J Am Acad Dermatol* 1997;37:422-9.
 97. Johnson TM, Sondak VK. A centimeter here, a centimeter there: Does it matter? *J Am Acad Dermatol* 1995;33:532-4.
 98. Mundun A, Murray DR, Herda SC, Eshima D, Shattuck LA, Vansant JP, et al. Early stage melanoma: lymphoscintigraphy, reproducibility of sentinel node detection, and effectiveness of the intraoperative gamma probe. *Radiology* 1996;199:171-5.
 99. Cohen MH, Ketcham AS, Felix EL, Li SH, Tomaszewski MM, Costa J, et al. Prognostic factors in patients undergoing lymphadenectomy for malignant melanoma. *Ann Surg* 1977;186:635-42.
 100. Albertini JJ, Cruse CW, Rapaport D, Wells K, Ross M, DeConti R, et al. Intraoperative radiolymphoscintigraphy improves sentinel lymph node identification for patients with melanoma. *Ann Surg* 1996;223:217-24.
 101. Starzl TE, Zinkernagel RM. Antigen localization and migration in immunity and tolerance. *N Engl J Med* 1998;339:1905-13.
 102. Veronesi U, Adamus J, Bandiera DC, Brennhovd IO, Caceres E, Cascinelli N, et al. Inefficacy of immediate node dissection in stage I melanoma of the limbs. *N Engl J Med* 1977;297:627-30.
 103. Veronesi U, Adamus J, Bandiera C, Brennhovd IO, Caceres E,

- Cascinelli N, et al. Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremity. *Cancer* 1982;49:2420-30.
104. Sim FH, Taylor WF, Pritchard DJ, Soule EH. Lymphadenectomy in the management of stage I malignant melanoma: a prospective randomized study. *Mayo Clin Proc* 1986;61:697-705.
105. Balch CM, Soong S, Bartolucci AA, Unist MM, Karakousis CP, Smith TJ, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg* 1996;224:255-66.
106. Morton DL, Wen DR, Wong JM, Economou JS, Cagle LA, Storm FK, et al. Technical details of intra-operative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;127:392-9.
107. Krag DN, Meijer SJ, Weaver DL, Loggie BW, Harlow SP, Tanabe KK, et al. Minimal-access surgery for staging of malignant melanoma. *Arch Surg* 1995;130:654-8.
108. Reintgen D, Cruse CW, Wells K, Berman C, Fenske N, Glass F, et al. The orderly progression of melanoma nodal metastases. *Ann Surg* 1994;220:759-67.
109. McCarthy WH, Thompson JF, Uren RF. Invited commentary. *Arch Surg* 1995;130:659-60.
110. Leong SP, Steinmetz I, Habib FA, McMillan A, Gans JZ, Allen RE, et al. Optimal selective sentinel node dissection in primary malignant melanoma. *Arch Surg* 1997;132:666-73.
111. Van der Veen H, Hoekstra OS, Paul MA, Cuesta MA, Meijer S. Gamma probe-guided sentinel node biopsy to select patients with melanoma for lymphadenectomy. *Br J Surg* 1994;81:1769-70.
112. Rees WV, Robinson DS, Holmes EC, Morton DL. Altered lymphatic drainage following lymphadenectomy. *Cancer* 1980;45:3045-59.
113. Leong SL, Achtem TA, Miller JR, Nguyen LH, Ituarte P, Steinmetz I, et al. Clinical significance of melanoma micrometastasis to sentinel lymph nodes and other high risk factors [abstract]. *Proc Am Soc Clin Oncol* 2000;19:551A.
114. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 1996;14:7-17.
115. Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of Intergroup trial E1690/S9111/C9190. *J Clin Oncol* 2000;18:2444-58.

AVAILABILITY OF JOURNAL BACK ISSUES

As a service to our subscribers, copies of back issues of the *Journal of the American Academy of Dermatology* for the preceding 5 years are maintained and are available for purchase from Mosby until inventory is depleted. The following quantity discounts are available: 25% off on quantities of 12 to 23, and one third off on quantities of 24 or more. Please write to Mosby, Subscription Customer Service, 6277 Sea Harbor Dr, Orlando, FL 32887, or call 800-654-2452 or 407-345-4000 for information on availability of particular issues and prices. If unavailable from the publisher, photocopies of complete issues may be purchased from Bell & Howell Information and Learning, 300 N Zeeb Rd, Ann Arbor, MI 48106, (313)761-4700.