Malignant Melanoma Microstaging
History, Premises, Methods, Problems, and Recommendations—A Call for Standardization

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Microstaging is the application of microscopic measurements, qualitative and/or quantitative, to malignant tumors for the purpose of predicting a patient's prognosis.

In the span of 40 years, the pathology literature concerning the spectrum of entities grouped under the term "malignant melanoma" has flourished. Although often overlooked and left unacknowledged, the fundamental concepts of melanoma pathology were made possible by the minds of only a handful of observers. If not for these individuals, deaths from undiagnosed and untreated malignant melanoma would possibly remain unchecked.

Hundreds of articles written over this timespan have focused on the clinical and histological criteria for the diagnosis of malignant melanoma. Few authors, however, have addressed the specific problems facing the pathologist in microstaging melanomas,[1,2] despite the fact that microstaging is requested as a critical part of every pathology report in order for the subsequent course of a patient's life to be managed. Indeed, many studies make no mention of any specific problems encountered in obtaining measurements by Clark's or Breslow's methods.

Because standardized microstaging is the fundamental base from which any rational clinicopathologic databases might emerge, it is essential that every malig-

This paper was read in part by Dr. Hurt at the Second Regional Dermatopathology Colloquium co-sponsored by Ain Shams University and the International Society of Dermatopathology, Cairo, Egypt, September 18, 1992.

nant melanoma be measured the same way every time. Thus, we will attempt to address this critical issue by reviewing its historical development, the biologic considerations, and the technical problems that are often faced in standardization of measurements. Finally, we offer criteria that we believe should serve as guidelines for the future standardization of melanoma microstaging.

HISTORICAL BACKGROUND

Allen and Spitz were among the first to identify a class of melanomas that were more indolent than others.[3] In their words:

> It is to be concluded, therefore, that while it is impossible to predict which lesions will prove fatal, the odds are sizeable that the patient with the superficial melanocarcinoma, in locations other than the mucosa, has considerably more chance of survival than the patient with the more deeply invasive tumor. Moreover, it was noted that it apparently takes only a *small added increment of depth* of invasion to cause sharp deterioration in the group prognosis. [italics ours]

Thus, the identification of a qualitative relationship between the location of the melanoma within the dermis and patient survival was discovered. However, neither "superficial" nor "small added increment of depth" was explicitly defined by the authors. Their figures indicate tumors that were in the papillary dermis and with overlying pagetoid spread. Some of these patients had local metastasis.

It would require the studies of Lund and Ihnen,[4] Petersen et al,[5] Mehnert and Heard,[6] and Clark et al[7] to focus more precisely on the relationship of tumor depth to patient survival. Although their combined observations resulted in a better understanding of this relationship, the systems were not interchangeable, and the terminology was not easily transposed. A table combining classifications based on tumor depth within various levels of invasion in the skin is given in Table 1 to illustrate this point. If one standardizes the location of the tumor in the skin to that of patient outcome, however, one may observe that these studies resulted in similar conclusions. To wit: melanomas within the

TABLE 1. MALIGNANT MELANOMA MICROSTAGING: SYSTEMS PRIOR TO BRESLOW

Level in Skin	Allen and Spitz, 1953	Lund and Ihnen, 1955	Petersen et al, 1962	Mehnert and Heard, 1965	Clark et al, 1969
Epidermis	No designation	No designation	1	0	I
Papillary dermis	Superficial?	1	2	1	II and III
Reticular dermis	Deep?	2	"Tumor formation" 3	2	IV
Subcutis	No designation	3	No designation	3	V

epidermis and papillary dermis had an excellent prognosis (approaching 80 percent survival at 5 years) compared with the relatively poor prognosis of patients whose tumors were located in the reticular dermis and subcutis (approximately 40 percent and 15 percent, respectively).[3–7] This is depicted graphically in Figure 1.

In contrast to the earlier studies, however, the study of Clark et al[7] stratified melanomas *within* the papillary dermis. This resulted in the identification of a subpopulation of patients who not only had a relatively poor outcome but also had tumors filling the papillary dermis while sparing the reticular dermis (Fig. 2).

Breslow, in 1970,[8] approached microstaging in a different way. He hypothesized that total tumor volume, not just anatomic location within the skin or tumor diameter, might be related to prognosis, especially in small melanomas that metastasized:

> Though there is a roughly inverse relationship between the diameter of the lesion and survival, very small lesions have recurred or metastasized. One possible reason for the lack of reliability of tumor size in estimating prognosis may be that studies to date have considered size in only two dimensions and have neglected tumor volume.

Breslow recognized that precise volume could not be obtained directly; thus, he suggested the following indirect method:

> To measure tumor volume it is necessary to know the surface area of the tumor, but in this retrospective study we only know the maximal diameters of the lesions. By measuring the maximal thickness of the lesions we can calculate the maximal cross-sectional area, which should be roughly proportional to the volume of the tumor.

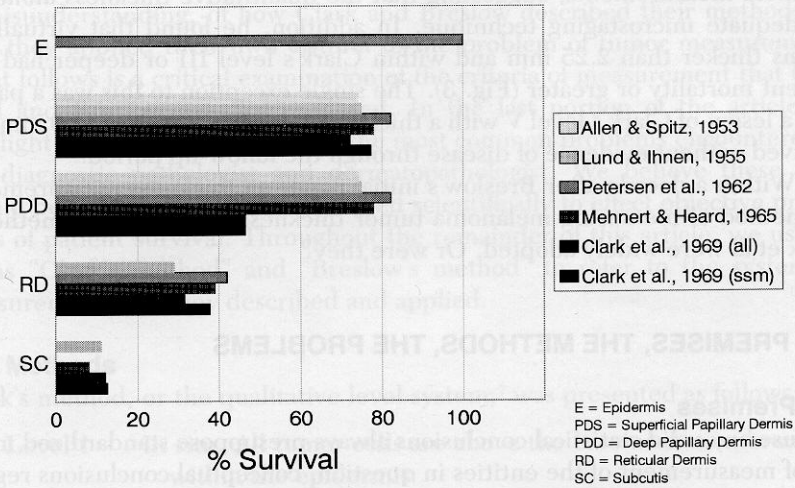

Figure 1. Anatomic location of melanoma versus survival.

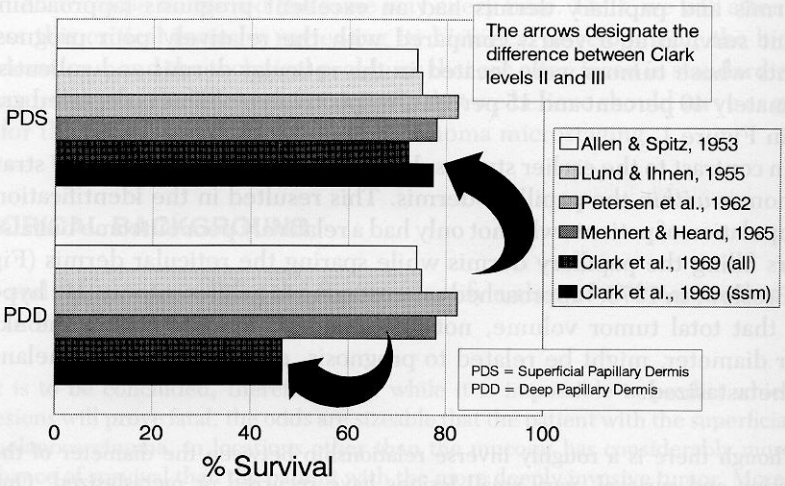

Figure 2. Anatomic location of melanoma versus survival. Difference between Clark levels II and III.

Breslow's data suggested, with some inconsistencies probably owing to limited sample size, that the estimated cross-sectional area of a tumor, as well as tumor thickness, was inversely proportional to disease-free patient outcome. More importantly, he discovered that none of his patients died from tumor if their lesions were less than 0.76 mm in thickness (none of which was deeper than Clark's level III). When he stratified his data in relation to the data of Clark's method, Breslow discovered that the tumor thickness principle could also be applied, generally, *within* each of Clark's levels. Even so, there was considerable overlap in prognosis *between* Clark's levels when stratified for thickness measurements, suggesting that the quantitative thickness *alone* was an adequate microstaging technique. In addition, he found that virtually all lesions thicker than 2.25 mm and within Clark's level III or deeper had a 50 percent mortality or greater (Fig. 3). The single exception to this was a patient with a lesion of Clark's level V with a thickness between 2.26 and 3.00 mm who survived without evidence of disease through the follow-up period.

Within a decade after Breslow's initial paper on thickness measurements, his method of measuring melanoma tumor thickness as well as the method of Clark et al were widely adopted. Or were they?

THE PREMISES, THE METHODS, THE PROBLEMS

The Premises

Because any valid statistical conclusions always presuppose standardized methods of measurement of the entities in question, conceptual conclusions regarding the prognosis of malignant melanomas have rested on the premises of

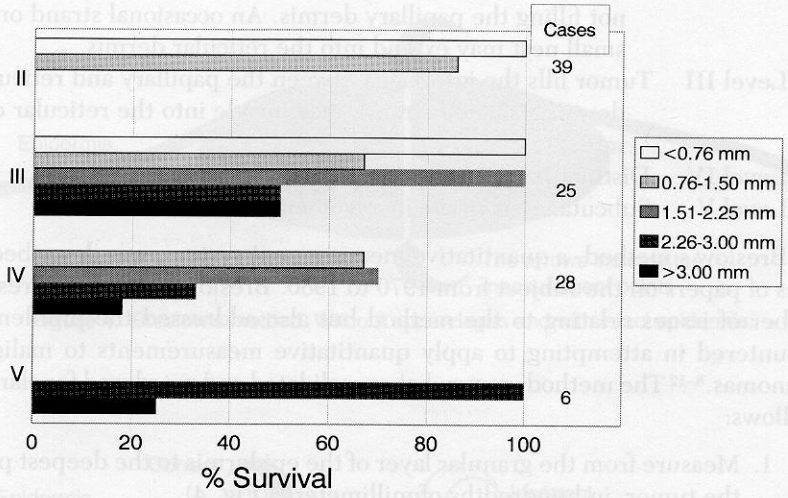

Figure 3. Clark's and Breslow's methods versus survival. *(From Breslow A. Ann Surg. 172:902, 1970.)*

melanoma microstaging set forth by Clark et al and Breslow. Their inductive conclusions, which were based on the empirical observations of hundreds of cases, resulted in qualitative (Clark) and quantitative (Breslow) classification criteria. It was thus critical that one be able to apply these criteria consistently to cases. Failure to do so would result in data linked to a false model of melanoma prognosis. After reviewing the literature and confronting many problems in the microstaging of malignant melanomas, it is our opinion that several sources of potential error exist in the present model, although the basic approach is sound. The cause of these potential errors lies in the understanding, or misunderstanding, of how Clark and Breslow described their methods and how they applied their own criteria to the problem of tumor measurements. What follows is a critical examination of the criteria of measurement that Clark et al and Breslow actually proposed. In the last portion of the article, we highlight the areas we believe are the most common problems encountered by the diagnostic pathologist and dermatopathologist. We believe these areas should be better clarified, then studied scientifically to effect objective predictions of patient survival. Throughout the remainder of this article, we use the terms "Clark's method" and "Breslow's method" to refer to the systems of measurement that they described and applied.

The Methods

Clark's method, or the qualitative level system,[7] was presented as follows:

Level 1 In situ. All tumor cells are above the basement membrane within the epidermis.

Level II Papillary dermal involvement including periappendageal, but

not filling the papillary dermis. An occasional strand or small nest may extend into the reticular dermis.

Level III Tumor fills the interface between the papillary and reticular dermis. Isolated strands may invade into the reticular dermis.

Level IV Distinct invasion into the reticular dermis.

Level V Subcutaneous tissue involvement.

Breslow's method, a quantitative measurement system, was described in a series of papers on the subject from 1970 to 1980. Breslow not only addressed a number of issues relating to the method but also addressed the problems he encountered in attempting to apply quantitative measurements to malignant melanomas.[8–12] The method, somewhat consolidated and reordered for clarity, is as follows:

1. Measure from the granular layer of the epidermis to the deepest part of the tumor, in hundredths of millimeters[9] (Fig. 4).
2. Measure at right angles to the surface of the skin above the tumor[9] (Fig. 5).
3. If the thickest part of the tumor is ulcerated, measure from the bottom of the ulcer bed to the deepest part of the tumor (Fig. 6).[9]
4. Do not measure epidermal junctional theques of melanoma. These are not considered to be invasive.[11]
5. If one exists, do not include a benign nevus under the melanoma in the measurement.[11]
6. Do not include in the measurement deep nests of melanoma in close proximity to the epidermal appendages because they are most likely adventitial tumor cells[11] (Fig. 7).
7. Disregard atypical melanocytes that are in a column perpendicular to the epidermis. They are probably periappendageal[11] (Fig. 8).
8. Include in the measurement any melanoma tumor satellites deep to the tumor proper[12] (Fig. 9) (see below for further elaboration on this point).
9. Do not measure recurrent or metastatic disease.[9]
10. If the skin surface is uneven so that a perpendicular measurement cannot easily be achieved, construct a perpendicular at either periphery of the tumor and construct a line bisecting the intersection of both perpendiculars to measure the thickest part of the tumor[12] (Fig. 10).

Breslow stratified breakpoints into five groups[8]:

<0.76 mm
0.76 to 1.50 mm
1.51 to 2.25 mm
2.26 to 3.00 mm
>3.00 mm

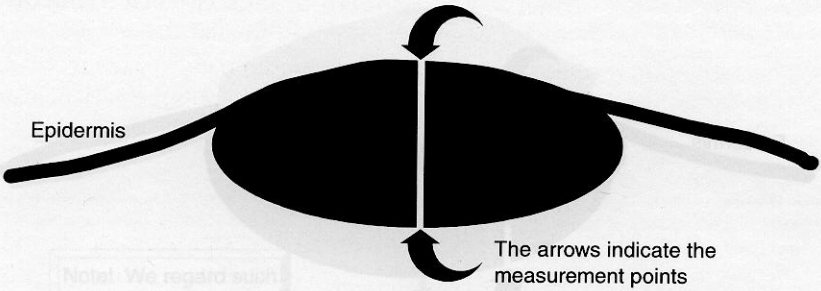

Figure 4. Breslow's method. Without appendages and with intact epidermis.

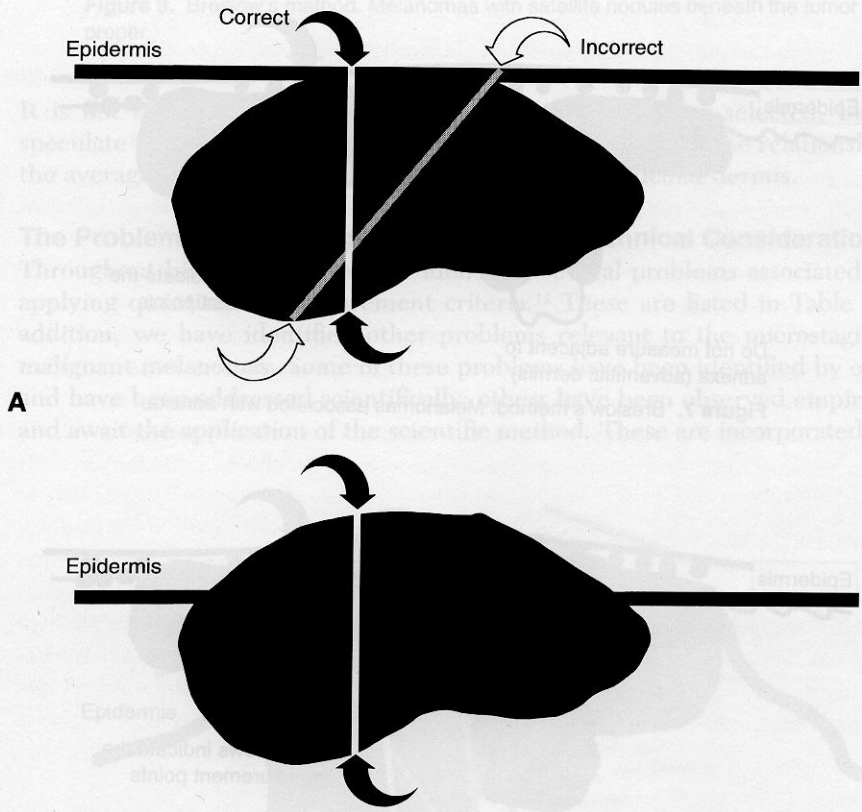

Figure 5. Breslow's method. Measure tumor perpendicular to the surface. **A.** This asymmetrical tumor is still measured at right angles to the surface. **B.** This asymmetrical tumor is identical to that in **A,** but it protrudes above the epidermis. The measurement also includes the exophytic portion of the tumor.

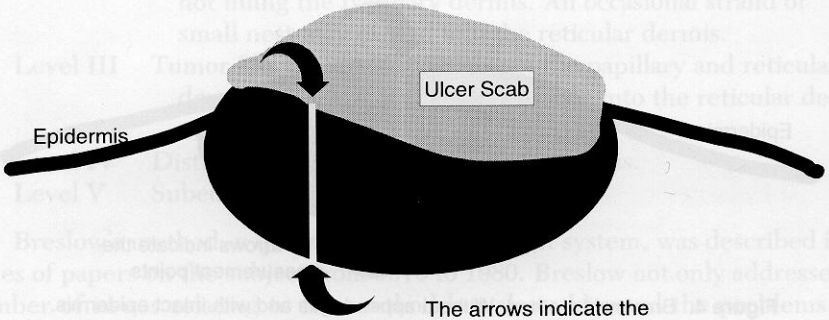

Figure 6. Breslow's method. Measuring ulcerated melanomas.

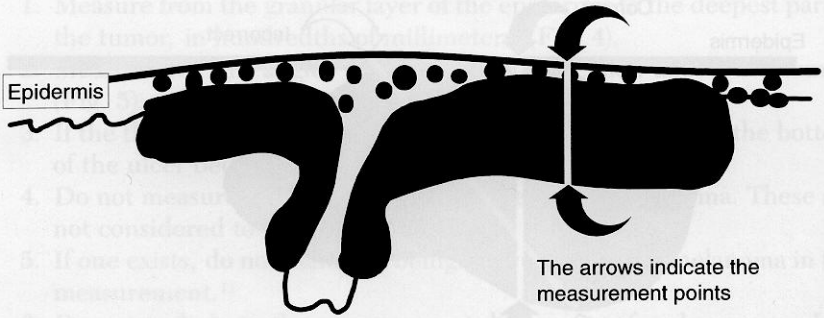

Figure 7. Breslow's method. Melanomas associated with adnexa.

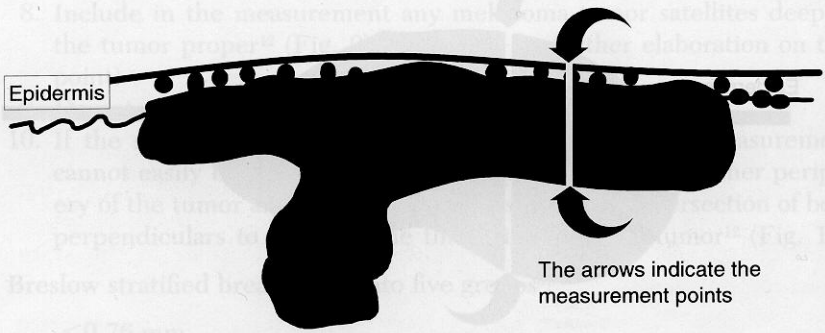

Figure 8. Breslow's method. Melanomas with a perpendicular column of tumor cells.

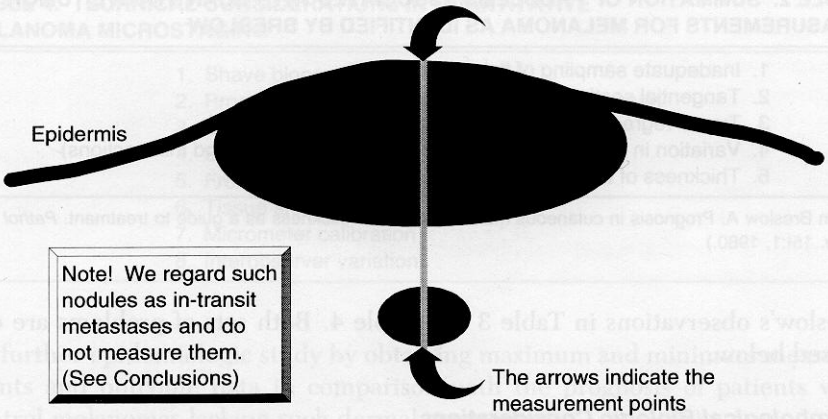

Figure 9. Breslow's method. Melanomas with satellite nodules beneath the tumor proper.

It is not known why these particular measurements were selected, but we speculate that they may have been chosen because of their close relationship to the average breakpoints between the papillary and reticular dermis.

The Problems: Morphological/Biologic and Technical Considerations

Throughout his writings, Breslow identified several problems associated with applying quantitative measurement criteria.[12] These are listed in Table 2. In addition, we have identified other problems relevant to the microstaging of malignant melanomas. Some of these problems have been identified by others and have been addressed scientifically; others have been observed empirically and await the application of the scientific method. These are incorporated with

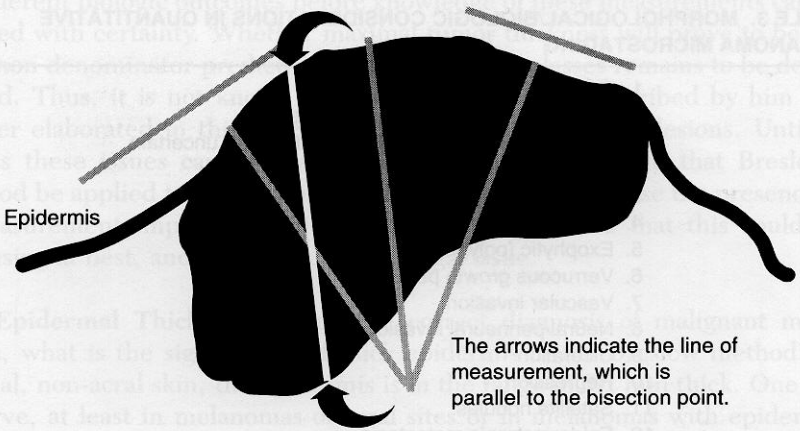

Figure 10. Breslow's method. Bisection technique for irregular epidermis.

TABLE 2. SUMMATION OF PROBLEMS ASSOCIATED WITH QUANTITATIVE TUMOR MEASUREMENTS FOR MELANOMA AS IDENTIFIED BY BRESLOW

1. Inadequate sampling of the tissue
2. Tangential sectioning and/or embedding
3. Tumor regression: Where does one measure?
4. Variation in histological technique (the effects of thick and thin sections)
5. Thickness of the epidermis

(From Breslow A. Prognosis in cutaneous melanoma: Tumor thickness as a guide to treatment. *Pathol Annu.* 15l:1, 1980.)

Breslow's observations in Table 3 and Table 4. Both sets of problems are discussed below.

Morphological/Biologic Considerations

Correct Diagnosis and Atypical Melanocytic Lesions. The most important problem associated with the microstaging of malignant melanoma is that of identifying the lesion in question *as* malignant melanoma *versus* some other pathologic class of lesion. This also becomes important if one observes a lesion similar to malignant melanoma in the epidermis and superficial dermis, while the deep component is similar to that of a melanocytic nevus. The assessment of thickness measurements in these lesions hinges on the differentiation of the "nevus" component from the "melanoma" component. The area in which to measure in these lesions is often unclear because of the difficulty in the identification of the entire lesion as malignant melanoma with a small cell phenotype versus a malignant melanoma associated with a melanocytic nevus that presumably arose out of the nevus. Because of this problem, one should not classify these lesions under the usual measurement system. These should be set aside

TABLE 3. MORPHOLOGICAL/BIOLOGIC CONSIDERATIONS IN QUANTITATIVE MELANOMA MICROSTAGING

1. Correct diagnosis
   Coexistence of melanocytic nevus
   Atypical melanocytic lesions, unknown or uncertain
2. Epidermal thickness
3. Microinvasion
4. Periadnexal growth patterns
5. Exophytic (polypoid) tumor
6. Verrucous growth patterns
7. Vascular invasion
8. Neural/perineural invasion
9. Ulceration
10. Regression
11. Satellite nodules
12. Epidermotropic metastasis
13. Local recurrence

TABLE 4. TECHNICAL CONSIDERATIONS IN QUANTITATIVE MELANOMA MICROSTAGING

1. Shave biopsy
2. Proper sectioning or "cutting-in" of the specimen
3. Diagonal cutting of the tissue
4. Sections too thick or not standardized
5. Frozen section methods
6. Tissue shrinkage
7. Micrometer calibration
8. Interobserver variation

for further epidemiologic study by obtaining maximum and minimum measurements and outcome data in comparison with the prognosis of patients with control melanomas lacking such dermal components.

The other question with respect to the correct diagnosis concerns atypical melanocytic lesions, that is, melanocytic lesions that are difficult to classify and of which the biologic potential is incompletely known. Names such as "minimal deviation melanoma,"[13] "atypical melanocytic lesion, biology uncertain," and other names have been used. An objective presentation of the morphological and biologic spectrum of this class of lesions has not been preformed, in our opinion.

Of course, one may measure *any* atypical melanocytic lesion with a micrometer. This does not mean, however, that any such measurements have been objectively established to gauge a patient's prognosis. For instance, it is not clear how the measurements of atypical melanocytic lesions of the mucosa, atypical melanocytic lesions with similarity to blue nevi (so-called "malignant blue nevus"), or atypical melanocytic lesions characterized by distinct dermal nodules without epidermal connections correlate with patient outcome. Further refinements of such concepts must be clearly established to explain similar or different biologic outcomes before knowledge of these measurements can be applied with certainty. Whether maximal tumor thickness will prove to be the common denominator predicting outcome in these classes remains to be determined. Thus, it is not known if Breslow's method, as described by him and further elaborated in this article, will be applicable to such lesions. Until or unless these issues can be resolved, we do not recommend that Breslow's method be applied to such lesions in pathology reports because the presence of a measurement implies biologic malignancy. We believe that this could be confusing at best, and a potential medicolegal issue.

Epidermal Thickness. Given the correct diagnosis of malignant melanoma, what is the significance of thick epidermis in the Breslow method? In normal, non-acral skin, the epidermis is in the range of 0.1 mm thick. One can observe, at least in melanomas of acral sites or in melanomas with epidermal hyperplasia, that the epidermis may be twice or more as thick as non-acral epidermis. This translates into thickness measurements of at least 0.2 mm or

thicker before the area containing tumor cells is measured. This could conceivably amount to a significant difference in thickness measurements of some lesions (Fig. 11), especially thin tumors. It would play less of a role in thicker melanomas. Breslow considered this parameter and found it difficult to assess:

> The amount of epidermal hyperplasia is variable and may, in thin tumors, make up a large part of the measured thickness of the lesion. There is no simple, quantitative way to deal with this problem, and for such lesions, we simply note that there is a minimal invasion of the papillary dermis and that much of the measured thickness is due to epidermal hyperplasia.[12]

We believe, however, that quantitative epidermal thickness should be investigated further as a source of differences in prognosis of patients with malignant melanoma.

Periadnexal Dermis. Breslow and Clark both proscribed the measurement of tumors directly adjacent to columns of melanocytes perpendicular to the epidermis. When one observed such changes, they were presumed to signal the presence of adnexal structures that would falsely increase the measurement. We agree with this interpretation (compare Figures 7 and 8). In addition, skin containing numerous adnexa can present a significant problem owing to the fact that increased adnexal density may prevent one from easily finding an area free of adnexa. This observation is empirical, however. We are not aware of any scientific investigations that address this specific question.

Polypoid Melanoma. Breslow advocated that the thickest portion of the melanoma be measured regardless of whether it was endo- or exophytic, a recommendation consistent with his measurements of thinner melanomas[12] (Fig. 12). In doing so, he avoided the problem faced by Elder et al in arbitrarily assigning a level III to polypoid melanomas.[14] Because polypoid melanomas, thickness for thickness, are similar in biology to nonpolypoid melanomas,[15,16] the

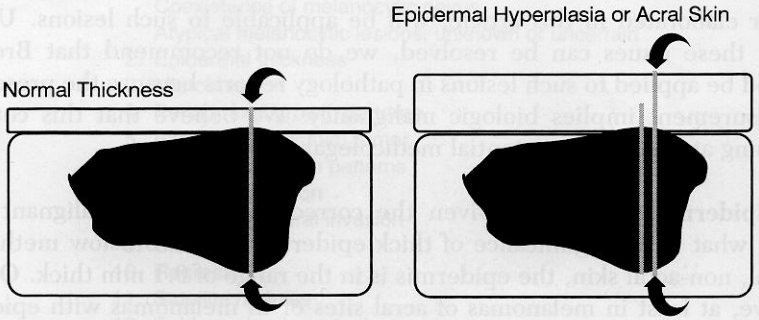

Figure 11. Epidermal thickness. Effect of differences in epidermal thickness on quantitative tumor measurement in melanoma microstaging.

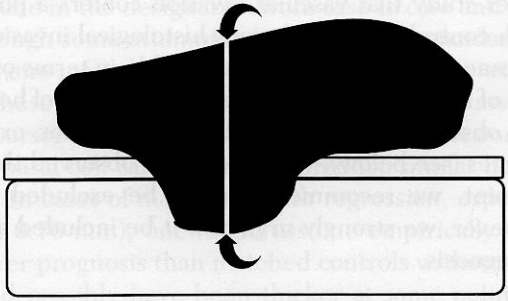

Figure 12. Polypoid melanoma. Melanoma microstaging.

application of Breslow's method in such lesions is a more rational approach that avoids an arbitrary microstage starting point.

Verrucous Melanoma. Verrucous changes in malignant melanoma have been reported to confer no significant differences, thickness for thickness, in prognosis than other patterns of melanoma.[17] However, the measurement methods by which this conclusion was drawn are obscure. While such tumors may often be quite thick at the time of diagnosis, we do not believe that the question of measurements has been addressed in an objective manner for this class of lesions. Because verrucous melanomas may have marked variance in thickness from zone to zone (Fig. 13), we believe that scientific investigations of such lesions should be undertaken to develop objective criteria for applying measurements consistently.

Vascular Invasion. Vascular invasion may be observed occasionally in melanomas with clearly established vertical growth. Vascular invasion is rarely observed in thin lesions, especially those less than 1.0 mm thick. It is probable that vascular invasion is a biologic attribute associated with thickness of the tumor; that is, as the tumor grows it is able to gain access to vessels. In one study the presence of vascular invasion was directly proportional to thickness.[18]

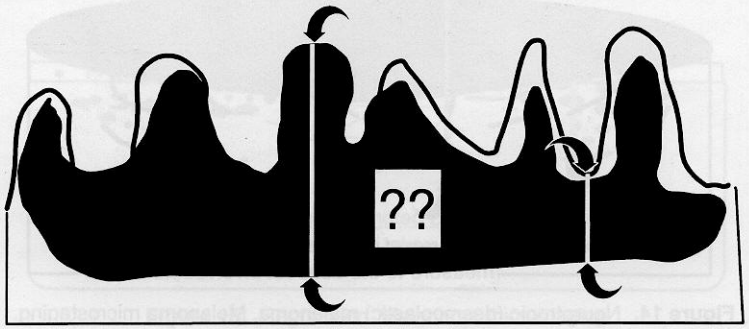

Figure 13. Verrucous malignant melanoma. Melanoma microstaging.

There is evidence from another study that vascular invasion confers a poorer prognosis when compared with controls lacking obvious histological invasion.[19]

With regard to the significance of microstaging this variable in terms of the Breslow method, we are aware of no study that addresses the question of how to regard vascular invasion if it is observed below the main body of tumor, except in studies of microscopic satellites (see below). We have never observed this in our practice. As a starting point, we recommend that it be excluded as a numerical measurement. However, we strongly urge that it be included as an independent line under the diagnosis.

Neural and Perineural Invasion. The main problem in evaluating neurotropic melanomas, apart from making the correct diagnosis, is in assessing how deeply the tumor invades, because the deep portions may be infiltrative and difficult to differentiate from fibrosis.[20] Since the growth pattern is neurotropic, special studies, such as S100 protein, may be helpful as an adjunct in highlighting the deepest areas for measurement. Although Breslow did not specifically address this growth pattern in his measurement classification, we suggest that the deepest tumor-involved nerve be included in the measurement (Fig. 14). We recognize that this suggestion is empirical, but it follows logically from Breslow's principles. To better understand the nature of these lesions, perhaps both deep perineural involvement and measurement of the main tumor bulk should be scientifically investigated to compare the respective outcomes.

Regression. Regression refers to the clinical phenomenon of partial or complete diminution or disappearance of the melanoma as the result of an inflammatory host response. Histologically, minimal criteria for the diagnosis of regression require evidence of melanoma associated with "skip" or diminished areas composed of fibrosis and a prominent vascular component, host response with melanophages, or combinations of these findings. The criteria for regression have not been established for a wide spectrum of lesions. There is great

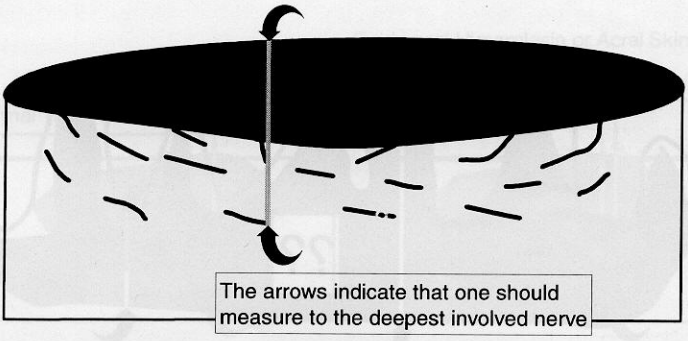

Figure 14. Neurotropic (desmoplastic) melanoma. Melanoma microstaging.

latitude in the designation from case to case and from pathologist to pathologist, although some attempts at establishing a standard have been made.[21] Occasionally, one may observe evidence of regression without an associated melanoma. In these cases, it cannot be unequivocally assumed that melanoma was the precursor lesion because other pigmented lesions such as seborrheic keratoses and basal cell carcinoma may produce similar host responses.

In cases of melanoma with regression, especially the thin melanomas (less than 0.76 mm), one might assume empirically that such lesions would have a poorer prognosis than matched controls without regression, because the former could possibly have been thicker at some point before regression. One study concluded that this was the case.[22] Five of 23 patients (21.7 percent) with metastasis whose lesions had evidence of regression and were less than 0.76 mm thick were compared with 2 of 98 patients (2 percent) with metastasis but without regression. Stated another way, 71 percent of the metastatic melanomas were observed in lesions with regression. Although this study had a relatively small sample, it suggested that regression may be an important finding. Other studies with larger series of patients, however, have reported no significant differences in outcome of patients with such lesions compared with those with tumors without evidence of regression.[23–26] Thus, we believe the evidence is much stronger that regression in thin melanomas is *not* a significant finding denoting a poor prognosis for the patient.

Other than measurement of the tumor, Breslow had no specific recommendations for microstaging these lesions. We have observed that it may be difficult to distinguish between the melanocytic and a marked melanophagic component in such lesions. We do not recommend special stains for such tumors, however, especially if there is a heavy host response. In our empirical experience, using commonly available markers such as S100 protein, we have been unable to differentiate with certainty tumor cells from dendritic cells in the inflammatory zones. We recommend that in melanomas with regression, measurements be taken only where tumor is unequivocally present (Fig. 15). The presence of regression should be noted in the report, but should not be included as a separate line under the diagnosis.

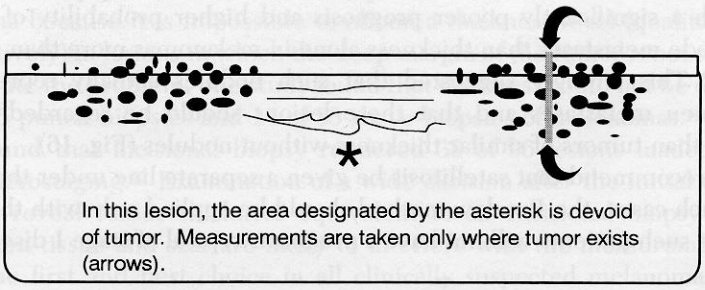

Figure 15. Regression. Melanoma microstaging.

Ulceration. In assessing ulcerated malignant melanoma, Breslow advocated that the tumor be measured from the deep portion of the ulcer, not the superficial portion of the scale crust (Fig. 6). He did not specifically state why he chose this particular method. We agree with his decision because the measurement of nonviable tissue would establish an arbitrary standard, although it is tempting to speculate on the hypothetical prognosis of extrapolated data.

The presence of ulceration over a malignant melanoma has been the subject of many studies. Most have regarded ulceration as an independent predictor of poor prognosis when compared with nonulcerated matched controls.[27] However, no theoretical mechanism has adequately explained the reason for poor prognosis. One overlooked, albeit speculative, hypothesis for this difference in prognosis is that ulcerated tumors would have most likely been thicker if they had not ulcerated. If they had been thicker, the statistical prognosis would have been worse, likely owing to a richer tumor vasculature. Thus, when one *measures* an ulcerated melanoma by the Breslow method, this hypothesis presumes that one is measuring a thinner tumor than it would have been had it not ulcerated, while the biology of such a tumor would be that of a more virulent stage. To validate such a hypothesis, knowledge of the preulcerated thickness of such tumors would be required. Because of the clinical nature of such tumors, ie, they *present* as clinical ulcers, such a prospective study is unlikely to be performed in humans.

Thus, we concede that we are limited in our current understanding of the biology of ulcerated melanomas, but we recognize that ulceration is an important prognostic parameter. We recommend that ulceration, if present, be reported as a separate line under the diagnosis.

Satellite Nodules. Breslow regarded subtumoral satellite nodules as a legitimate portion of the primary melanoma and advocated that they be included in quantitative microstage measurements.[12] However, his assertion was not made with any reference to observations of patient outcome, nor did he address the issue of peritumoral satellite nodules. This has been studied subsequently. The investigators defined a satellite as a cluster of melanoma cells separated from the melanoma and measuring more than 0.05 mm in diameter. They discovered that satellite nodules, whether involving vessels or not, were associated with a significantly poorer prognosis and higher probability of regional lymph node metastases than thickness alone in melanomas more than 1.50 mm thick.[28,29] This strongly suggested that such nodules actually represent intraspecimen metastases and that these lesions should be regarded as more ominous than tumors of similar thickness without nodules (Fig. 16).

We recommend that satellitosis be given a separate line under the diagnosis. In such cases, the Breslow method should be applied only with the knowledge that such patients will not have a prognosis typical of stage I disease.

Epidermotropic Metastases. Epidermotropically metastatic melanoma was not specifically addressed by Breslow, other than his general statement not to

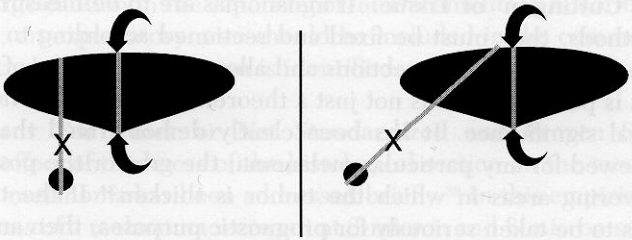

Figure 16. Satellite nodules. Melanoma microstaging. **Note:** In both examples, the satellite should not be measured as part of the Breslow method. Instead, these nodules should be regarded as micrometastases and reported as such. Arrows indicate where the actual measurements should be taken, but these patients should not be regarded as having classic stage I disease.

measure metastatic malignant melanoma.[9] The importance of identifying epidermotropically metastatic melanoma is that its histological attributes are similar to those of primary melanomas.[30] Thus, special care must be taken in all cases to obtain appropriate clinical information to avoid the mistaken classification of metastatic lesions as primary tumors.

Recurrent Melanoma. To be considered a recurrent malignant melanoma, a previously known melanoma must have been documented at the specific site in question. Otherwise, the assertion is speculative. Unfortunately, the presence of recurrence is associated with a prognosis similar to that of regional or systemic recurrence.[31] Thus, at this point, we do not recommend that the thickness of recurrences be reported, as the measurement does not appear to be specific in staging the patient's disease. Further scientific study to compare the prognosis of patients with thick versus thin recurrences may be helpful in answering this question.

Technical Considerations

Shave Biopsy. This is an obvious problem in the initial evaluation of a melanoma because it is impossible to obtain a thickness level (qualitatively or quantitatively) in lesions in which the deep margin of the tumor is not removed. To illustrate the problem, one study found that thickness could not be measured in 6 of 25 punch biopsies and 14 of 33 shave biopsies of melanomas.[32] Another study found that incisional biopsy rendered 38 of 96 lesions inadequate for initial microstaging.[33] Examination of a wide excision after the initial diagnosis may not reveal tumor thickness equivalent to an excisional biopsy because granulation tissue and scar are likely to interfere with the measurement. Certainly, the first and best choice in all clinically suspected melanomas is total excision if at all possible. Thus, we strongly recommend excisional biopsies on all clinically suspected malignant melanomas.

Proper "Cutting in" of Tissue. If melanomas are to be measured by standardized methods, they must be fixed and sectioned according to techniques that produce the best possible sections and allow for the review of as much of the tumor as is possible. This is not just a theoretical matter, but rather one of great practical significance. It has been clearly demonstrated that the more sections reviewed for any particular melanoma, the greater the possibility one has of discovering areas in which the tumor is thicker.[34] If the thickness of melanomas is to be taken seriously for prognostic purposes, then an underestimation of thickness should be of grave concern by any diagnostician. We agree completely with those who advocate multiple transverse sections of the lesion after fixation[1] as opposed to cruciate or perpendicular sectioning methods. To take this a step further, however, we also advocate the use of a special "rule of halves," explained elsewhere, in order to obtain the thinnest possible and best oriented sections for routine use.[35]

Diagonal Cutting of Tissue. Breslow stated that maloriented tissue could present a potential problem.[10,36,37] However, he did not believe that it was very significant and stated that a gross error of up to 22.5 degrees would increase the measurement by only 8 percent. In other words, a 1-mm lesion cut at 22.5 degrees from the correct plane of sectioning would appear as 1.08 mm. However, errors of greater than 22.5 degrees result in considerable error. A 1 mm lesion cut at a bias of 45 degrees would appear as 1.41 mm (41 percent error) (Fig. 17).

Malorientation may occur because of improper cutting of the tissue by the pathologist, by improper embedding, or both. We observe maloriented melanomas from time to time and do not believe that we can discern which cases originate from improper cutting or improper embedding. A scientific study into this question would be useful.

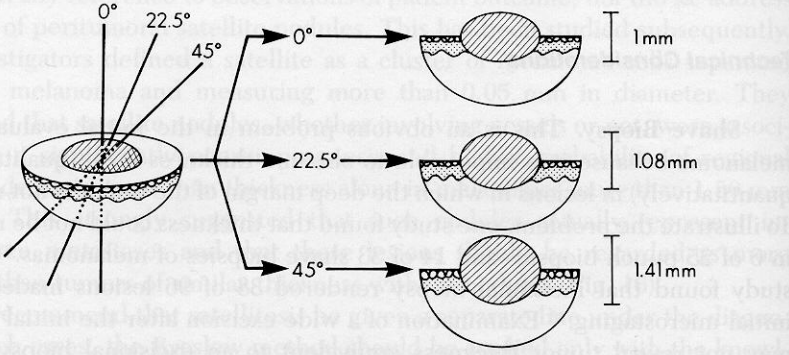

Figure 17. The effect of diagonal cutting or embedding on the apparent thickness of the melanoma. By employing standard trigonometric methods, one may observe that minimal error in the final measurement occurs even with a diagonal cut of 22.5 degrees. Marked differences, however, are noted when greater diagonal cutting error occurs.

We urge caution in the reporting of measurements in maloriented cases. At minimum, an explanatory note should be included in the comments section of the report when malorientation is identified.

Sections Too Thick or Not Standardized and Frozen Section Methods. The effect of thickness of the histological section on the measurement of a malignant melanoma has been addressed briefly.[38] In this empirical study, adjacent sections of a melanoma were cut at 3-micron and 8-micron sections. The 3-micron section measured 20.5 percent thicker than the 8-micron section, suggesting a possible relationship between section thickness and cross-sectional tumor thickness. While this observation raised an interesting question, it was hardly objective because it was not a controlled study. It is tempting to suggest that thinner sections are more amenable to stretching when the paraffin ribbon is produced and in the water bath during preparation of histological slides. It is also well known that melanomas may vary from section to section. Adjacent sections, even in melanomas that are standardized for fixation and sectioning, may not measure the same. Thus, a better model needs to be proposed to properly study this potential pitfall.

The application of frozen sections to the measurement of malignant melanoma is also fraught with problems, owing principally to the difficulty in handling the tissue consistently and obtaining acceptable sections for measurement.[39] However, at least one study suggests that for thin melanomas, less than 1.0 mm, frozen section methods may be appropriate to achieve adequate staging.[40] As a note of caution, we consider it imperative that correlation of frozen section methods to the formalin-fixed biopsies be established, because many clinicians do not have the expertise or the time to request frozen sections of every suspected melanoma for the purpose of microstaging. Objective standardization of any frozen section technique will require reproducible data in multiple studies as well as a willingness by surgeons and pathologists to participate.

Tissue Shrinkage. A few reports have stated that tissue shrinkage or thick sections can have a major influence on the measured thickness of the tumor, varying from 20 to 30 percent for fixation shrinkage[38] and 20 percent thicker measurements for thick sectioning.[41] The significance of these artifacts has been refuted by other authors.[42,43] We recommend a systematic investigation into this question, recognizing that, by the nature of the clinical and pathologic practice of melanoma pathology, it is a difficult one to answer. At the very least, standardized fixation and sectioning techniques could help to minimize any potential problem.

Micrometer Calibration. As simple as it is to calibrate an ocular micrometer, it might be a startling revelation for the pathologist to actually calibrate each lens with a standard rule before making an attempt to measure the tumor in question. Frequently, the indicated power on the lens may be said to be calibrated for a certain measure; however, because of variations in the manufacture

of the microscope, as well as wear and tear on the ocular micrometer, eyepiece, or other moving parts of the microscope, these calibrations may be in error. For example, a 1-mm scale with 100 subdivisions and 10× ocular and objective will correspond to a measured 1 mm under the microscope if calibration is correct. However, greater than 5 percent error could easily occur if the assumption is made that there is no need for this calibration before thickness measurements are determined. Therefore, we believe that it is imperative that microscopes used to measure melanomas be calibrated with a precision standard. A useful starting point would be one's use of the Vernier scale on the moving stages of most quality microscopes. One may measure to the nearest 0.1 mm using such a scale. Considering the multiple judgments involved in establishing *where* to measure a melanoma, measuring to the nearest 0.1 mm is probably sufficient for the measurement. That is, we find it difficult to believe that measuring to the nearest 0.01 mm is a realistic measurement of the true thickness considering the numerous potential sources for error enumerated in this article. Even so, measuring to the nearest 0.01 mm will probably remain the written standard because of medicolegal considerations.

Interobserver Variation. Breslow[10] claimed that good agreement in measuring maximal thickness was easily obtained by several pathology residents with 2 to 4 years of training. His data showed that initially, up to 15 percent error occurred between his measurement and the residents' until he gave instruction. Subsequent to this, all residents measured the tumor thickness within 5 percent of his measurement. A high interobserver correlation for tumor thickness has also been reported by others.[44,45]

Regardless of this reported agreement, our empirical experience is that of wide variation between the way we measure melanomas compared with the measurements of those who consult us. If this is any indication of the general practice of microstaging, we have cause to be concerned. At a minimum, pathologists should strive to agree on how they obtain measurements for melanomas. While this will not ensure knowledge of patient outcome, it is the first step in the acquisition of such knowledge.

RECOMMENDATIONS FOR THE FUTURE

Because of the variables identified above, we recommend that the following guidelines be applied to the microstaging of malignant melanoma.

1. *The biopsy should be excisional.* Incisional or shave biopsy is to be discouraged, with certain exceptions for clinical impracticality. Do not report thickness on shave biopsies unless the tumor is completely included in the biopsy. An alternative is to report a minimum thickness with a cautionary comment regarding incomplete sampling of the tumor.

2. *Gross room technique.* Use a transverse approach, such as the rule of halves or similar technique that includes the full silhouette of the tumor. Do *not* use a perpendicular (cruciate) cutting technique. Make sections at 2 mm intervals and include only one section of the tumor per block under ideal conditions, or at most not more than two pieces per block. If the clinician needs fresh tumor for marker studies or immunotherapy, use the rule of halves on fresh tissue and select the grossly thinner section for the clinical studies. Fix the sliced tumor between cork for several hours to flatten it for sectioning in such cases.
3. *Glass slides.* Obtain three or four tissue sections per tumor block in order to observe the full extent of the tumor.
4. *Diagnostic accuracy.* Be certain that the lesion is truly a melanoma before assigning a microstage. If in doubt, do *not* assign a microstage because microstaging a melanocytic lesion implies that the lesion is a melanoma.
5. *Calibration of microscope.* Make certain that the micrometer is calibrated with a standard for the ocular and each objective used in making measurements. Measure all portions of the melanoma to find the thickest level (a handheld 2 mm calibrated lupe will suffice for making a "rule of thumb" sighting prior to the final measurement).
6. *Reporting of measurement.* Report the thickest section of the tumor after reviewing all the slides on the case. Measure to the nearest tenth of a millimeter (eg, 1.7 mm); we doubt the validity of using measurements to the nearest hundredth of a millimeter. A microscope stage Vernier (standard on most professional-grade microscopes) is a handy and practical way to secure this measurement. Consideration of medicolegal precedents may require estimation to the nearest 0.01 mm.
7. *Microscopic satellites.* Regard satellite nodules, either subtumoral or peritumoral, as intraspecimen metastases. If present, do not measure the tumor under the banner of stage I disease.
8. *Epidermotropic metastases.* Do not measure if the lesion is an epidermotropic metastasis.
9. *Recurrent melanoma.* Do not measure because these lesions have a prognosis similar to that for regional or systemic disease. Further studies may change this approach.
10. *Neural or perineural invasion.* If a nerve is involved by tumor, the measurement should include the deepest involved nerve. Future studies should compare the main bulk of these tumors to the deepest involved nerves.
11. *Verrucous melanoma.* In cases of verrucous melanoma, take an average from peak to trough. Report maximal, minimal, and mean. Such lesions require further systematized study to develop objective standards.
12. *Associated morphologic variables.* Record, if present, ulceration and vascular invasion as a separate line under the diagnosis. Record regres-

sion in the body of the report but do not include it as a separate line under the diagnosis.

13. *Artifacts.* Observe and record any technical artifacts that might interfere with the measurement. If the measurement is compromised, record this fact in the report.
14. *Standardization and agreement.* Share cases with each other to develop intradepartmental agreement among pathologists. While this will not necessarily determine which melanomas will kill, agreement is the first step in developing objective guidelines to apply to melanomas in order to be understood from institution to institution.

CONCLUSION

Malignant melanoma is a diagnosis that includes a wide spectrum of morphological and biologic entities. Because of this fact, researchers must continue to focus on the identification of attributes helpful in explaining the natural history of this spectrum of lesions. Microstaging is only one such attribute, but it is essential to one's objective understanding of prognosis, especially in the light of newer staging systems that use quantitative measurement criteria in mathematical equations for prognostic indices.[46] If measurement methods are not standardized and understood widely by those applying the criteria in such prognostic systems, the resultant data will be arbitrary and, therefore, meaningless.

With further honing of current observations and their application to more and more detailed and rigorous logically constructed studies, perhaps someday it will be possible to conclusively identify biochemically or genetically the persons at risk for melanoma. Whether such technology will ever be possible or necessary, only time will tell. But even if such technologies *can* be developed, it will still be necessary to properly classify melanomas histologically *when* they are discovered, unless new technologies can be devised that would classify such lesions on a purely physiological, rather than a morphological, basis. For the present and the foreseeable future, morphological microstaging is certain to remain with us, an issue firmly grounded in the principles and practice of classic anatomic pathology.

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1994

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