Malignant Melanoma

Prognostic Significance of "Microscopic Satellites" in the Reticular Dermis and Subcutaneous Fat

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A review of the microscope slides of the primary tumors for 596 patients with clinical Stage I melanoma revealed that primary lesions displayed two distinct patterns of invasion: 1) single cell invasion with direct extension of the main body of tumor into the reticular dermis or subcutaneous fat, and 2) invasion with "microscope satellites" (*i.e.* discrete tumor nests > 0.05 mm in diameter, that were separated from the main body of the tumor by normal reticular dermal collagen or subcutaneous fat). The five-year disease free survival rate for 95 patients with "microscopic satellites" was 36% ± 6%. This is in contrast to a five-year disease free survival rate of 89% ± 2% for 501 patients without these satellites ($p = 4.3 \times 10^{-29}$, generalized Wilcoxon test). "Microscopic satellites" (present vs absent) was comparable to histologic ulceration in its additive prognostic effect to tumor thickness (Breslow).

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IN THE LATE 1960s, Clark and co-workers[7] described a microstaging system for melanoma. This system encompassed their concept of the developmental biology of melanoma and also allowed one to determine the probability of death due to melanoma for the individual patient. In 1970, Breslow[5] published his version of a melanoma microstaging system. He correlated measured thickness (in millimeters) of the primary melanoma with prognosis. Using an ocular micrometer, he found an increasing risk of death from melanoma with increasing thickness of the primary lesion. Both of these microstaging systems are now widely used; they have had an impact on melanoma surgical and medical treatment.

Within the last five years, there have been at least six studies[1,6,9,12,16,18] comparing the relative merits of these two microstaging systems. All six studies demonstrated that thickness was superior to level of invasion in predicting outcome. Three of the studies[6,12,18] demonstrated a small but additive effect of level of invasion once thickness was known. In contrast, three of the studies[1,9,16] demonstrated no added effect for level of invasion. Schmoeckel and Braun-Falco[16] argued that a combination of mitotic rate and thickness constituted the best "prognostic index." More recently Balch et al.[2] analyzed a largely retrospective series of 248 clinical Stage I melanoma patients using a Cox multivariate analysis[8]; they found that ulceration was superior to any other histologic parameter in its additive effect of thickness.

To better understand the reasons for the variation in the results noted above, pathologists at New York University Medical Center and Massachusetts Gen-

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eral Hospital repeatedly reviewed microscope slides from a prospective study group of 596 patients with clinical Stage I melanoma seen at the above institutions between 1972 and 1977. One of the pathologists involved in this study noticed that some melanomas had discrete microscopic satellites, separate from the main body of the tumor, in the reticular dermis and subcutaneous fat. The present study is an analysis of the prognostic usefulness of this finding. Preliminary results indicate that this finding is a better prognostic addition to thickness than ulceration. These three variables in combination (thickness, microscopic satellites, and ulceration) comprise a powerful prognostic model.

Patients and Methods

Six hundred forty-three patients with primary cutaneous malignant melanomas were evaluated consecutively, and entered prospectively into a study group at one of two institutions, New York University Medical Center or the Massachusetts General Hospital, from September 1, 1972 through May 30, 1977. Characteristics of this population have been described previously.[17] All patients had either an intact primary lesion when first examined, or had their primary lesions removed within 30 days prior to entry into the study. All patients were treated surgically by wide excision and primary closure, or by wide excision followed by split thickness grafting. In addition, some patients had elective lymph node dissections. Detailed pathology protocols were completed prospectively by pathologists at the respective institutions. Histologic sections were then reviewed by one pathologist.

Six hundred six of these patients (94%) had no clinical evidence of metastatic disease (clinical Stage I). Of these 606 patients, microscope slides for detailed examination were obtained for 596 (98%) patients. These 596 patients are the subjects of this paper. Each patient was followed for evidence of recurrent disease at three month intervals or less for the first two years, at six month intervals for the next three years, and annually thereafter. The time interval to the last follow-up examination or time to recurrence was computed from the date of definitive surgery.

Disease-free survival at five years was computed according to the method of Kaplan and Meier.[14] Probability values for comparing two sets of life-table data in their entirety were determined using the generalized Wilcoxon test.[13]

Microscopic Satellites

One of the authors (TJH) noticed that some melanomas had discrete nests of melanoma cells clearly separated, by normal reticular dermal collagen or subcutaneous fat, from the main body of the tumor. Invasive tumors without these nests exhibited only single cell invasion. These single cells were usually contiguous with the main body of the tumor. To more clearly separate these two patterns of invasion, the nests were required to be noncontiguous with the main body of the tumor, and >0.05 mm in diameter. Slides were reviewed independently by two of the authors (TJH and CLD) without knowledge of the other's reading. There was a difference of opinion between these two authors on only six slides out of a total of 596 lesions studied, (1%). These six slides were assigned to one of the two invasion groups by the senior pathologist (MCM).

Thickness

Thickness was the dominant prognostic variable for patients with clinical Stage I melanoma in the multivariate analyses done by Eldh et al.,[12] Balch et al.,[2] E. Cox et al.,[9] and Day et al.[10,11] For this reason, stratification by thickness was done to determine whether or not there was any added prognostic effect of "microscopic satellites" to thickness. Thickness was measured using an ocular micrometer according to the method of Breslow. The thickness divisions tested were those used by Balch et al.[1] (*i.e.* ≤ 0.75 mm, 0.76–1.50 mm, 1.51–3.99 mm, and ≥4.0 mm).

Histologic Ulceration

The presence of microscopic satellites, as a prognostic factor, was tested against histologic ulceration to demonstrate the relative positions of these two parameters in the melanoma histologic hierarchy.

Histologic ulceration was determined using the criteria of Balch et al.[13] Because Little,[15] Eldh et al.[12] and Balch et al.[3] demonstrated a correlation of ulceration width, ulceration widths were measured using an ocular micrometer.

Results

Thickness and Ulceration (Tables 1 and 2)

Both ulceration and thickness were powerful prognostic indicators. In the present series, there was no difference in survival between patients with nonulcerated lesions and patients with lesions with ulceration widths ≤ 3 mm. Furthermore, there was no difference in survival for patients with lesions with ulceration widths of 3.01–6.0 mm, when compared with patients who had lesions with ulceration widths of >6.0 mm (Table 1).

TABLE 1. *Five-year Disease Free Survival for 596 Patients with Clinical Stage I Melanoma when Stratified by Width of Histologic Ulceration of the Primary Lesion*

	No Ulceration	0.1–3.0 mm	3.1–6.0 mm	>6.0 mm
Five-year disease free survival	89% (411)	86% (77)	45% (47)	45% (61)
*p = 0.4		no ulceration	vs	ulceration 0.1–3.0 mm
*p = 0.6		ulceration 3.1–6.0 mm	vs	ulceration > 6.0 mm
*p = 4.9×10^{-26}		ulceration ≤ 3.0 mm or no ulceration	vs	ulceration > 3.0 mm

% = per cent surviving free of disease for five years as determined by Kaplan-Meier actuarial life tables.
( ) = number of patients in each subgroup.
* Probability values as determined by a generalized Wilcoxon test.

Ulceration > 3.0 mm in width significantly improved prognostic information for lesions > 1.5 mm. There was, however, no added effect of ulceration width for lesions ≤ 1.5 mm in thickness (Table 2).

Thickness and Malignant Tumor Islands (Table 3)

The finding of microscopic satellites in the reticular dermis and subcutaneous fat was a powerful prognostic indicator. As was the case with ulceration, there was no added prognostic effect for this finding when the primary tumor thickness ≤ 1.5 mm. For lesions > 1.5 mm, however, the p values of the associated life tables indicated that this parameter was comparable to ulceration > 3.0 mm in width in its additive effect to thickness.

Thickness, Ulceration and Malignant Tumor Islands (Table 4)

Life tables with combinations of the above three variables indicate that more information was obtained by a combination of ulceration and "microscopic satellites" than from either alone, particularly over the thickness range of 1.51–3.99 mm.

Discussion

The data demonstrate the prognostic value of assessing the presence or absence of microscopic satellites in the reticular dermis and subcutaneous fat. This finding was comparable to ulceration in its additive prognostic effect to thickness for patients with lesions > 1.5 mm. The biologic meaning of this finding is unclear. It may represent in effect an "intraspecimen metastasis." Such intraspecimen metastases are then an indication of the existence of "extraspecimen metastasis."

Additional step sections may have demonstrated an increased incidence of these satellites; conversely, connections of the satellites to the main body of the tumor may have been found in some instances. This same argument could be made, however, for any other melanoma histologic parameter (*i.e.* additional step sections might increase the histologic ascertainment of ulceration and/or thicker lesions). Futhermore, determinations for this study were made on the same histologic sections that were originally used to formulate the official hospital record pathology reports. This finding then proved "usable" from a practical standpoint.

Comparisons With Ulceration (Tables 5 and 6)

The per cent of ulcerated lesions, in the present study, are remarkably similar to those published by Little,[15] Eldh et al.[12] and by Balch et al.[3] Furthermore, the survival rates in the present series by ulceration width were not significantly different than those pub-

TABLE 2. *Five-year Disease Free Survival Rate for 596 Patients with Clinical Stage I Melanoma when Stratified by Thickness and Ulceration > 3.0 mm in Width*

Thickness	No Ulceration or Ulceration Width ≤3.0 mm	Histologic Ulceration >3.0 mm in Width	p value*
≤0.75 mm	(168) 99.4% ± 0.6%	(0) —	—
0.76–1.50 mm	(172) 91% ± 2%	(7) 100%	0.4
1.51–3.99 mm	(128) 76% ± 5%	(47) 47% ± 10%	0.001
≥4.0 mm	(20) 50% ± 12%	(54) 34% ± 7%	0.1
Total	(488) 89% ± 2%	(108) 45% ± 6%	4.9×10^{-26}

* Generalized Wilcoxon Test.

TABLE 3. *Five-year Disease Free Survival for 596 Patients with Clinical Stage I Melanoma when Stratified by Thickness and Presence or Absence of "Microscopic Satellites" in the Reticular Dermis or Subcutaneous Fat*

Thickness	Satellites Absent	Satellites Present	p value*
≤0.75 mm	(168) 99.4% ± 0.6%	—	—
0.76–1.50 mm	(144) 92% ± 3%	(7) 75% ± 22%	0.95
1.51–3.99 mm	(134) 77% ± 4%	(41) 40% ± 11%	0.004
≥4.0	(27) 60% ± 11%	(47) 28% ± 6%	0.002
Total	(501) 89% ± 2%	(95) 36% ± 6%	4.3×10^{-29}

* Generalized Wilcoxon test.

lished by Little[15] or by Eldh et al.[12] The survival rates, published by Balch et al., by ulceration widths were appreciably lower than either the present study or the other two studies (*i.e.* Little or Eldh et al.). The reasons for this are not entirely clear. Balch et al. did not examine microscope slides of the primary tumor for approximately one-third of their entire series. Thus, one cannot be certain that the reported results accurately reflected the results that would have been obtained with 100% pathology. In conclusion, the findings of the present study as well as those of Little[15] and Eldh et al.[7] concur with Balch et al., (*i.e.* ulceration is an important prognostic variable for melanoma). However, the combined data suggest that the magnitude of the effect of ulceration is probably less than emphasized by Balch et al.[3] This conclusion is further supported by the multivariate analysis of E. Cox et al.,[9] who found no added prognostic effect of ulceration. A Cox multivariate analysis on the 596 clinical Stage I patients in the NYU-MGH series yielded results similar to E. Cox et al. when ulceration width was not considered (unpublished observation).

There was no difference in survival rates between those patients with nonulcerated lesions versus those patients with ulcerated lesions ≤ 3.0 mm in width. Those patients with ulceration widths 3.1–6.0 mm had survival rates comparable to those patients with ulceration widths > 6.0 mm. These findings suggest that a lesion should not be considered to be "ulcerated" unless it has an ulceration width > 3 mm; and there would appear to be no prognostic advantage for wider ulceration widths. These recommendations should, of course, be considered tentative pending reports from other centers. However, the remarkable similarities for prognosis by ulceration width between the present study and the results reported by Little[15] and Eldh et al.[12] would suggest that separation at an ulceration width of 3.0 mm may be reproducible.

These data would indicate that thickness, ulceration, and "microscopic satellites" complement each other in predicting outcome for clinical Stage I melanoma patients (particularly for patients with primary lesions 1.51–3.99 mm). It has been suggested by Balch et al.[2] that this latter subgroup of patients (i.e. those with lesions 1.5–3.99 mm in thickness) might benefit from elective regional node dissections (ERND). Currently, there are plans under way to perform a randomized study of ERND on such patients.[4] If such a study is undertaken, it would seem essential to use the presence or absence of "microscopic satellites" as a stratification variable to insure adequate randomization and interpretation of such a study.

Data and discussion for level of invasion were purposely left out for the following reasons: first, the six studies cited above,[1,6,9,12,16,18] comparing level of invasion with thickness, all demonstrated thickness to be better than level of invasion for predicting outcome. While three of the six studies[6,12,18] demonstrated some added effect for level of invasion, the magnitude of

TABLE 4. *Five-year Disease Free Survival for 596 Patients with Clinical Stage I Melanoma when Stratified by Thickness, Ulceration >3.0 mm in Width, and Presence or Absence of "Microscopic Satellites" in the Reticular Dermis or Subcutaneous Fat*

Thickness	No Ulceration or Ulceration <3.0 mm Wide; Satellites Absent	Ulceration >3.0 mm Wide; Satellites Absent	No Ulceration or Ulceration Width ≤3.0 mm; Satellites Present	No Ulceration Width >3.0 mm; Satellites Present
<0.75 mm	(168) 99.4% ± 0.6%	—	—	—
0.76–1.50 mm	(165) 92% ± 2%	(7) 100%	(7) 75% ± 22%	—
1.51–3.99 mm	(102) 83% ± 4%	(32) 59% ± 10%	(26) 47% ± 14%	(15) 29% ± 14%
≥4.0 mm	(11) 69% ± 15%	(16) 56% ± 14%	(9) 33% ± 16%	(38) 26% ± 7%

TABLE 5. *Proportion of Melanoma Patients According to Ulceration Width*

Ulceration Width	Little[15]	Eldh et al.[12]	Balch et al.[3]	Present Study
None	88 (65%)	213 (66%)	134 (61%)	411 (69%)
≤6 mm	25 (18%)	75 (23%)	59 (27%)	124 (21%)
>6 mm	23 (17%)	36 (11%)	26 (12%)	61 (10%)
Total	136	324	219	596

this effect was relatively small in all three reports. There seemed to be little reason for continuing this "level-thickness" debate. Second, melanomas with tumor nests in the reticular dermis and subcutaneous fat will, possibly, be interpreted by pathologists determined to continue using levels of invasion as a special subset of Level IV and Level V lesions. The following alternate interpretation is proposed by the authors: Some thick (>1.5 mm) and/or deeply invasive (Levels IV or V) melanomas display well formed microscopic satellites (nests) in the reticular dermis and/or subcutaneous fat; these satellites are not contiguous with the main body of the tumor. The metastatic potential of such lesions is significantly higher than tumors of equal thickness (>1.5 mm) or level of invasion (IV or V) without these satellites.

Finally, the real test for the prognostic value of "microscopic satellites" will be determined by a Cox multivariate analysis of the entire NYU-MGH series of 596 clinical Stage I patients. Such an analysis should test not only histologic, but also clinical variables. An analysis of this type was not done in the present study, because it was the purpose of this study only to describe the finding of microscopic satellites and to demonstrate its relative value when compared with two other excellent melanoma histologic prognosticators.

TABLE 6. *Five-year Survival Rate by Width of Histologic Ulceration*

Ulceration Width	Little[15]	Eldh et al.[12]	Present Study	Balch et al.[3]
None	(88) 89%	(213) 92%	(411) 89%	(134) 74%
≤6 mm	(25) 84%	(75) 67%	(124) 70%	(59) 44%
>6 mm	(23) 30%	(36) 43%	(61) 45%	(26) 5%
Total number of patients	136	324	596	219

References

1. Balch CM, Murad TM, Soong S, et al. A multifactorial analysis of melanoma. I. Prognostic histopathological features comparing Clark's and Breslow's staging methods. Ann Surg 1978; 188:732–742.
2. Balch CM, Soong S, Murad T, et al. A multifactorial analysis of melanoma. II. Prognostic features of clinical Stage I disease. Surgery 1979; 86:343–351.
3. Balch CM, Wilkerson JA, Murad TM, et al. The prognostic significance of ulceration of cutaneous melanoma. Cancer 1980; 45:3012–3017.
4. Balch CM. Personal communication.
5. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 1970; 172:902–908.
6. Breslow A, Cascinelli N, van der Esch EP, Morabito A. Stage I melanoma of the limbs: assessment of prognosis by levels of invasion and maximum thickness. Tumori 1978; 64:273–284.
7. Clark WH, From L, Bernardino EA, Mihm MC, Jr. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 1969; 29:705–715.
8. Cox DR. Regression Model and Life Tables. J R Stat Soc 1972; B34:187–220.
9. Cox E, Shingleton WW, Martel J, et al. Specific active immunization in melanoma: prognostic factors. Proceedings of the American Association for Cancer Research, 1980; 521, May 28–31.
10. Day CL, Sober AJ, Lew RA, et al. Malignant melanoma patients with positive nodes and relatively good prognoses: microstaging retains prognostic significance in clinical Stage I melanoma patients with metastases to regional nodes. Cancer 1981; 47:955–962.
11. Day CL, Sober AJ, Kopf AW, et al. Prognostic model for clinical Stage I melanoma of the upper extremity: the importance of anatomic subsites in predicting recurrent disease. Ann Surg 1981; 193:436–440.
12. Eldh J, Boeryd B, Peterson L-E. Prognostic factors in cutaneous malignant melanoma in Stage I. Scand J Plast Reconstr Surg 1978; 12:243–255.
13. Gehan EA. A generalized Wilcoxon test for comparing arbitrarily singlycensored samples. Biometrika 1965; 52:203–223.
14. Kaplan EL, Meier P. Nonparametic estimation from incomplete observation. J Am Stat Assoc 1958; 53:457–481.
15. Little JH. Histology and prognosis in cutaneous malignant melanoma. *In* McCarthy, WH (ed.) Melanoma and Skin Cancer, Proceedings of the International Cancer Conference, Sydney, Australia, VCN Blight, Government Printer, 1972; pp. 107–119.
16. Schmoeckel C, Braun-Falco O. Prognostic index in malignant melanoma. Arch Dermatol 1978; 114:871–873.
17. Sober AJ, Blois MS, Clark WH, et al. Primary malignant melanoma of the skin—1130 cases from the Melanoma Clinical Cooperative Group In Proceedings XV International Congress of Dermatology, Mexico, October, 1977. Excerpta Medica, Amsterdam, 1979.
18. Wanebo HJ, Woodruff J, Fortner JG. Malignant melanoma of the extremities: a clinico-pathologic study using levels of invasion (microstage). Cancer 1975; 35:666–676.
19. Day CL, Sober AJ, Kopf AW, et al. A prognostic model for clinical stage I melanoma of the lower extremity: Location on the foot is an independent risk factor for recurrent disease. Surgery 1981; 89:599–603.