The Prognostic Significance of Ulceration of Cutaneous Melanoma

CHARLES M. BALCH, MD, FACS,* JAMES A. WILKERSON, MD, TARIQ M. MURAD, MD, PHD, SENG-JAW SOONG, PHD, ANNA LEE INGALLS, RN, AND WILLIAM A. MADDOX, MD, FACS

Ulceration of a cutaneous melanoma on microscopic sections is an adverse prognostic finding. The five-year survival rate is reduced from 80% for non-ulcerated melanomas to 55% in the presence of ulceration for Stage I melanoma patients and from 53 to 12% for Stage II melanoma patients ($P < 0.001$). As a group, ulcerated lesions are thicker and more likely to have a nodular growth pattern. However, survival rates were still worse for ulcerated melanomas when matched with nonulcerated lesions for thickness and stage of disease. The width but not the depth of surface ulceration significantly correlated with survival. The median ulcer depth was 0.08 mm (range 0.01–1.2 mm). In those few lesions with ulcer craters more than 0.2 mm in depth, the melanomas were so thick they had the same poor prognosis regardless of whether thickness was measured to the base of the ulcer or to the top of the lesion. The Breslow microstaging method of measuring thickness is therefore a valid prognostic indicator, even for ulcerated lesions. The incidence of ulceration for the entire patient group ranged from 12.5% for melanomas <0.76 mm thickness to 72.5% for melanomas >4.0 mm thick (P of correlation = 0.001); from 12% for Level II invasion to 63% for Level V lesions ($P = 0.005$); from 23% for superficial spreading growth patterns to 49% for nodular and 74% for polypoid lesions ($P = 0.0001$); and from 27% for lesions with a heavy lymphocyte infiltration to 60% for minimal or absent host response ($P = 0.005$). There was no significant correlation with anatomic location, pigmentation of the melanomas, or with the patient's age and sex. Since ulceration appears to have such an important influence on survival rates, this parameter should be considered as a stratification criterion in clinical trials and accounted for when analyzing results of melanoma treatment.

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ULCERATION of a cutaneous melanoma was first identified as an adverse prognostic feature by Allen and Spitz in their classic description of melanoma histopathology.[1] Tompkins[19] corroborated this observation that same year, as have many others.[8,11,12,15,17,18] Some investigators, however, have not found this to be a critical variable affecting survival.[7,13,14]

In our series of patients, ulceration was one of the most important prognostic variables examined among thirteen factors affecting survival rates for both Stage I and Stage II melanoma.[2,4] As a result of this finding, we performed a more detailed analysis of the interrelationships between ulceration and other pathological and clinical factors. Because thickness of cutaneous melanomas is one of the most important prognostic variables,[4,10] and because the presence of ulceration is clearly associated with larger and thicker melanomas,[1,2,8,11,19] it is possible that ulceration was a dominant prognostic variable in our analysis only because thickness was underestimated when measured only to the crater base using the Breslow microstaging criteria.[5] We therefore measured the width and depth of the ulcer in these melanomas to determine their correlation with survival rates.

Patient Population and Methods

Patient Population

The University of Alabama Melanoma Registry now comprises over 500 melanoma patients treated at this institution during the past 20 years with clinical and pathological data recorded in a computerized format.

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From the Departments of Surgery, Pathology, Biostatistics, and the Comprehensive Cancer Center, University of Alabama Medical Center, University of Alabama in Birmingham, Birmingham, Alabama.

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Address for Reprint: Charles M. Balch, MD, Department of Surgery, 750 Lyons-Harrison Research Bldg., University of Alabama Medical Center, Birmingham, AL 35294.

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In this Registry are 250 cutaneous melanoma patients with adequate histopathological specimens for evaluation. Details of surgical treatment, histopathology, and clinical parameters for this series of patients have been published.[2,3,4] All pathological assessments and measurements were made by two pathologists (JAW and TMM) who had no knowledge of the patients' clinical course. Stage I patients had localized melanomas, Stage II patients had metastatic melanoma in regional lymph nodes, and Stage III patients had distant metastases.

Pathological Definitions

Ulceration was defined for this analysis as histologically identified necrosis and loss of the surface epithelium overlying the melanoma. Tumor invasion through the epidermis had a distinctively different histologic appearance and was not considered to be ulceration.

Tumor thickness was measured according to the criteria described by Breslow.[5,6] Using an ocular micrometer, the entire vertical height of the tumor was measured from the bottom of the melanoma to the granulosum layer of the overlying epidermis. For ulcerated melanomas, the tumor was measured to the base of the ulcer crater. In addition to these measurements, the depth of the ulcer crater and the width of surface ulceration was measured using the ocular micrometer in a subgroup of 85 ulcerated melanomas. An additional 24 melanomas with ulceration were not available for these measurements of the ulcer crater.

Statistics

Clinical and pathological information was computerized to facilitate data management and statistical analysis. Survival curves were calculated with the method of Kaplan and Meier. A generalized Wilcoxon test was used to determine the significant differences existing between the curves. Chi square tests were also employed as statistical assessment where appropriate. A multifactorial analysis of prognostic factors was employed using the regression model proposed by Cox.[9]

Results

Characteristics of Ulcerated Melanomas

Of the 250 cutaneous melanomas examined, 109 had evidence of ulceration. Their clinical and pathological characteristics are shown in Tables 1 and 2.

The incidence of ulceration was inversely correlated with the stage of disease (Table 1). Only 41% of patients with Stage I melanomas had ulcerated tumors whereas 70% of patients with Stage II disease had ulcerated lesions ($P < 0.01$). Ulceration clearly portended a poorer prognosis. Five-year survival rates for patients with ulcerated melanomas were significantly worse than for patients with non-ulcerated lesions both for Stage I melanoma patients (55 vs. 80%) and for Stage II melanoma patients (12 vs. 53%) (Fig. 1).

TABLE 1. Ulceration Subgrouped by Clinical Factors

	Pathological Stage I		Pathological Stage II	
	Ulceration (%)	No ulceration (%)	Ulceration (%)	No ulceration (%)
Number (%)	83 (40)	123 (60)	26 (70)	11 (30)
Median patient age	39	36	48	38
Sex				
Male	43 (44)	54 (56)	15 (68)	7 (32)
Female	40 (37)	69 (63)	11 (73)	4 (27)
Location				
Lower extremity	23 (42)	32 (58)	8 (89)	1 (11)
Upper extremity	23 (50)	23 (50)	4 (67)	2 (33)
Head and neck	12 (31)	27 (69)	3 (50)	3 (50)
Trunk	23 (37)	39 (62)	11 (69)	5 (31)

When compared to other histopathological features of melanomas, ulcerated lesions were generally thicker and were more deeply invasive than non-ulcerated lesions (Table 2). The presence of ulceration for the entire patient group ranged from 12.5% for melanomas <0.76 mm to 72.5% for melanomas >4.0 mm thickness (P value of correlation = 0.0001). Most (80%) ulcerated melanomas had a nodular or polypoid growth pattern but only 23% of superficial spreading growth patterns were ulcerated ($P = 0.0001$). Melanomas that had elicited little or no lymphocyte infiltration were generally ulcerated compared to those with a heavy lymphocyte infiltrate (60 vs. 27% respectively, $P = 0.005$). There was no significant correlation with anatomic location, pigmentation of the melanomas, or the patient's age and sex.

Depth of Ulceration and Melanoma Thickness

Although ulcerated melanomas as a group were significantly thicker than non-ulcerated melanomas, this finding did not completely explain the poor prognosis. Patients with ulcerated melanomas had lower survival rates even when compared to patients with non-ulcerated melanomas of the same thickness group (Fig. 2).

It is possible, however, that this poorer prognosis might be due to the microstaging method that measured the vertical dimension only to the ulcer base. As a result, the full thickness of the lesion might be underestimated. This possibility was examined in a subset

TABLE 2. Ulceration Subgrouped by Pathological Factors

	Pathological Stage I		Pathological Stage II	
	Ulceration (%)	No ulceration (%)	Ulceration (%)	No ulceration (%)
Number (%)	83 (41)	123 (59)	26 (70)	11 (30)
Median thickness	2.1 mm	1.2 mm	3.6 mm	2.9 mm
Median level of invasion	IV	III	IV	III
Growth pattern				
Nodular	54 (46)	63 (54)	15 (68)	7 (32)
Polypoid	14 (70)	6 (30)	9 (82)	2 (18)
Superficial spreading	12 (21)	45 (79)	2 (50)	2 (50)
Lentigo maligna	3 (33)	6 (67)	0	0
Pigmentation				
Present	68 (40)	101 (60)	16 (67)	8 (33)
Absent	12 (48)	13 (52)	8 (80)	2 (20)
Lymphocyte infiltration				
Absent to mild	34 (58)	25 (42)	13 (68)	6 (32)
Moderate to heavy	41 (32)	87 (68)	12 (75)	4 (25)

of 85 randomly selected melanomas with measurable ulcerations. The median depth of the ulcer crater was only 0.08 mm with a range of 0.02–1.2 mm (Fig. 3). Most lesions (88%) had an ulcer crater that measured less than 0.2 mm. Five of the six ulcerated melanomas with ulcer craters >0.2 mm had an overall thickness exceeding 4.4 mm when measured to the base of the ulcer crater (Table 3). The remaining patient had an intermediate thickness melanoma (1.7 mm) and a 0.3-mm ulcer crater. Here again, the crater depth would not have altered the prognostic significance of the overall thickness. Thus, the prognostic value of measuring tumor thickness by the Breslow microstaging criteria would not have changed in any of these patients even if the depth of the ulcer crater had been included in the measurement.

Width of Surface Ulceration

The width of surface ulceration was measured with an ocular micrometer. Melanomas with ulcerated areas less than 6 mm wide were thinner overall and had a more shallow ulcer crater than melanomas with more extensive loss of the surface epithelium (Table 4). The five-year survival rate was 44% for patients with ulcers less than 6 mm wide but only 5% for patients having melanomas with more extensive surface ulceration ($P < 0.001$). Both subgroups of patients with ulcerated melanomas had a lower survival than patients with non-ulcerated melanomas.

Multifactorial Analysis

In a previously published multifactorial analysis of melanoma, ulceration was a dominant prognostic

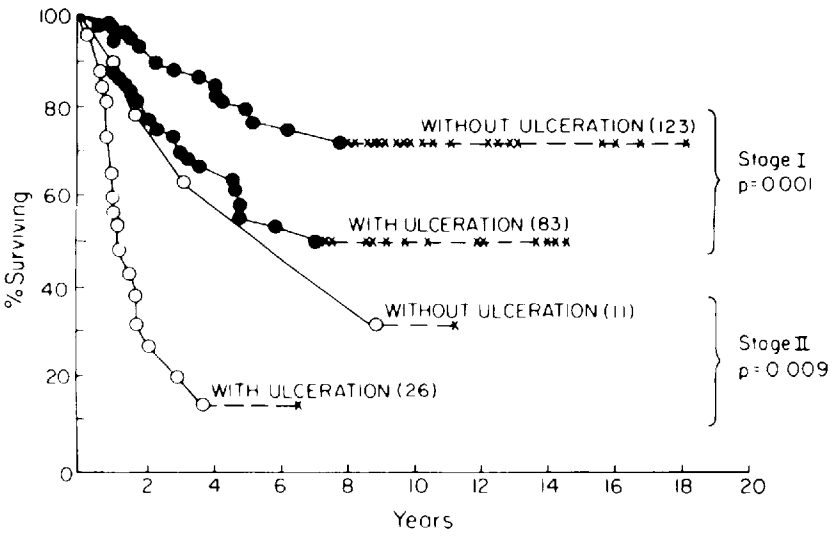

FIGURE. 1. Survival curves comparing ulcerated and non-ulcerated melanomas subgrouped by stage of disease.

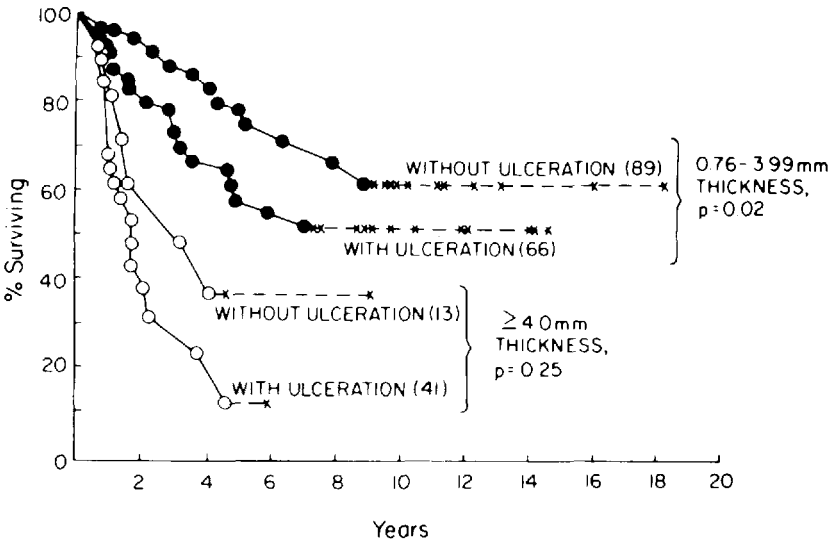

FIG. 2. Survival curves comparing ulcerated and non-ulcerated melanomas subgrouped by thickness groups.

factor ($P = 0.006$) when compared to 12 other parameters.[2] The Breslow criteria[5,6] for measuring melanoma thickness was used in this previous analysis. To examine whether this finding might have been influenced by an underestimation of the thickness in ulcerated melanomas, we added the depth of the ulcer crater to the thickness measurements and repeated the multifactorial analysis. Ulceration was still a dominant prognostic variable ($P = 0.001$) even when the total vertical dimension of the lesions was accounted for in ulcerated melanomas.

Discussion

By numerous criteria, ulceration of a cutaneous melanoma was an adverse predictor of survival even when the influence of other prognostic factors had been accounted for. Ulcerated melanomas were generally thick, nodular lesions with relatively little host inflammatory response around them. Polypoid lesions had a particularly high incidence of ulceration, both in this patient series and in the Queensland, Australia experience.[16] Although ulcerated lesions were thicker

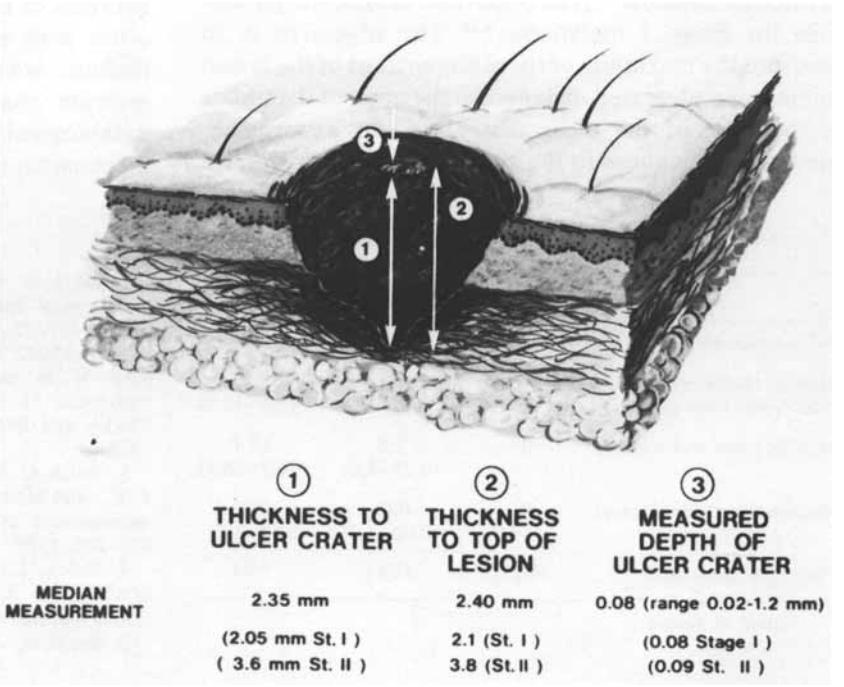

FIG. 3. Schematic depiction of ocular micrometer measurements from the ulcer crater to the base of the tumor in a plane perpendicular to the skin by the Breslow method (#1), from the highest point of the tumor to an estimated depth of maximum penetration (#2) and the measured depth of the ulcer crater (#3). Median measurements are shown for the entire series and subgrouped by stage of disease.

TABLE 3. Melanoma Thickness Associated with Ulcer Craters >0.2 mm in Depth*

Patient No.	Depth of ulcer crater (mm)	Melanoma thickness to ulcer base (mm)	Total thickness (mm)
510	0.3	1.7	2.0
152	0.8	4.4	5.2
133	0.5	6.3	6.8
162	1.2	6.0	7.2
157	0.3	8.0	8.3
101	1.2	8.0	9.2

* In 79 other ulcerated melanomas consecutively examined, the depth of the ulcer crater was ≤0.2 mm.

and more likely to be associated with metastatic disease, the poorer prognosis could not be accounted for simply by increased thickness because patients with ulcerated lesions still had lower survival rates when matched for stage of disease and for thickness groups.

Survival of patients with ulcerated melanomas strongly correlated with the width of the ulceration. In contrast, the depth of the ulcer crater did not correlate with survival. The prognostic significance of extensively ulcerated melanomas was most likely derived, in part, from a secondary correlation with the increased cross-sectional dimensions (width and thickness), although these measurements were not performed. Little[15] has previously observed that ulcer craters greater than 6 mm in width were associated with a worse prognosis.

The measurement of tumor thickness, as first described by Breslow[5,6] is an important prognostic parameter for Stage I melanoma.[4,10] The objective is to measure the maximum vertical dimensions of the lesion but in some ulcerated melanomas the apex of the tumor is the base of the ulcer crater. In our experience, measuring thickness to the base of the ulcer crater did not significantly underestimate overall tumor thickness. The median depth of a melanoma ulcer crater in our series was a mere 0.08 mm, a dimension that did not significantly influence prognosis resulting from the measured vertical height of the lesion. Moreover, those lesions with ulcer craters deeper than 0.2 mm were so thick overall that they had the same poor prognosis when the thickness was measured to the base of the ulcer crater or to the estimated apex of the melanoma. Thus, the presence of ulceration was still a dominant prognostic factor in a multifactorial analysis even when the depth of the ulcer was accounted for and the total vertical dimension of the melanomas was calculated. In a similar multifactorial analysis of 324 Stage I melanoma patients treated in Sweden, ulceration was also a dominant prognostic factor.[10]

TABLE 4. Width of Melanoma Ulceration

	None	0.1 to 6.0 mm	>6.0 mm
No. of patients	134	59	26
Median thickness to crater base (mm)	1.2 (0.2–8.1)*	2.1 (0.8–7.0)	3.5 (1.6–19.5)
Median ulcer width (mm)	0	2.6 (0.25–6.0)	10.7 (6.2–28.0)
Median ulcer depth (mm)	0	0.08 (0.02–1.2)	0.09 (0.04–1.2)
Five-year survival	74%†	44%†	5%†

* Range of values.
† $P < 0.001$.

The presence of ulceration overlying a melanoma reflects a more biologically aggressive tumor associated with a poorer prognosis. The mechanism for ulceration is poorly understood. Possibly the necrosis of the epidermis was caused by rapid tumor growth and interruption of the dermal vascular supply. Invasion of the epidermis was not a significant cause of surface ulceration in the lesions evaluated in this study. Physical trauma or abrasion also seems unlikely for several reasons. Some ulcerations were small punctate lesions in the center of a melanoma surrounded by normal, intact epidermis. Also, ulceration of the epithelium occurred over the entire surface of some polypoid melanomas, even in the unexposed areas on the undersurface of the mushroom-shaped tumor. Most significantly, inflammation and necrosis of the epidermis adjacent to the ulcer crater, often with a tapering or thinning of the intact epithelium, was a common finding. All of these features indicate that ulceration results from an inherent pathological property of the tumor rather than mechanical disruption.

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