A Multifactorial Analysis of Melanoma:

Prognostic Histopathological Features Comparing Clark's and Breslow's Staging Methods

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A multifactorial analysis was used to identify the dominant prognostic variables affecting survival from a computerized data base of 339 melanoma patients treated at this institution during the past 17 years. Five of the 13 parameters examined simultaneously were found to independently influence five year survival rates: 1) *pathological stage* (I vs II, p = 0.0014), 2) lesion *ulceration* (present vs absent, p = 0.006), 3) *surgical treatment* (wide excision vs wide excision plus lymphadenectomy, p = 0.024), 4) melanoma *thickness* (p = 0.032), and 5) *location* (upper extremity vs lower extremity vs trunk vs head and neck, p = 0.038). Additional factors considered that had either indirect or no influence on survival rates were clinical stage of disease, age, sex, level of invasion, pigmentation, lymphocyte infiltration, growth pattern, and regression. Most of these latter variables derived their prognostic value from correlation with melanoma thickness, except sex which correlated with location (extremity lesions were more frequent on females, trunk lesions on males). This statistical analysis enabled us to derive a mathematical equation for predicting an individual patient's probability of five year survival. Three categories of risk were delineated by measuring tumor thickness (Breslow microstaging) in Stage I patients: 1) *thin* melanomas (<0.76 mm) were associated with localized disease and a 100% cure rate: 2) *intermediate* thickness melanomas (0.76–4.00 mm) had an increasing risk (up to 80%) of harboring regional and/or distant metastases and 3) *thick* melanomas (≥4.00 mm) had a 80% risk of occult distant metastases at the time of initial presentation. The level of invasion (Clark's microstaging) correlated with survival, but was less predictive than measuring tumor thickness. Within each of Clark's Level II, III and IV groups, there were gradations of thickness with statistically different survival rates. Both microstaging methods (Breslow and Clark) were less predictive factors in patients with lymph node or distant metastases. Clinical trials evaluating alternative surgical treatments or adjunctive therapy modalities for melanoma patients should incorporate these parameters into their assessment, especially in Stage I (localized) disease where tumor thickness and the anatomical site of the primary melanoma are dominant prognostic factors.

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MELANOMA IS A CAPRICIOUS malignant neoplasm with many variables that seem to influence survival. Factors that have been described with prognostic value include such clinical parameters as stage of disease, sex, race, location and size of lesions, hair color, surgical treatment, pregnancy, and immunocompetence, as well as pathological parameters such as growth patterns, ulceration, blood vessel invasion or lymphocyte infiltration.[1,3,6,7,10,12,13,15,18,26] An important biological concept influencing prognosis is the correlation between increasing melanoma invasion into the skin and risk of metastases, as first described by Allen,[1] Lund,[17] Lane,[16] Peterson,[19] Mehnert[18] and others. In 1969, Clark and colleagues[5,6] defined levels of microinvasion and proposed a classification that has now been widely adopted. This system categorized melanoma by the maximum depth of penetration into different levels of the dermis or subcutaneous tissue. Breslow[3,4] suggested in 1970 that tumor thickness was a reliable criterion of prognosis. He measured the vertical dimensions of the melanoma in millimeters with an ocular micrometer as an alternative, and perhaps easier method for correlating melanoma invasion with survival. Others have corroborated that the histological level of melanoma invasion (as staged by Clark) and the measured lesion thickness (as advocated by Breslow) are very important deter-

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minants of survival and helpful guides for patient management.[7,9,10,12,13,22,26]

Most previous studies of melanoma patients have compared prognostic variables using single factor statistical analyses. Conflicting results from among these studies may have been influenced by intercorrelations of the variables examined, such as sex and melanoma location, or from additional factors that were not accounted for, such as tumor thickness. When numerous factors appear to influence survival rates, a multifactorial (or multivariate) analysis is necessary to delineate the dominant variables with independent predictive value. In this study, a multifactorial analysis was utilized to simultaneously compare 13 clinical and pathological features of melanoma. The computorized data base for this statistical analysis was compiled from a detailed retrospective/prospective study of over 339 patients treated at this institution during the past 17 years. This report focuses upon the histopathological features of 211 primary cutaneous melanomas for their potential prognostic value.

Patient Population and Methods

Patient Population

We examined the hospital records of 339 melanoma patients registered between 1960 to 1977 by the Tumor Registry or the Pathology Department at the University Hospital and the Veteran's Hospital. Patient groups excluded from this analysis included: 12 patients whose records contained insufficient clinical information, 13 patients who had nodal metastases from unknown primary sites, 13 patients with shave biopsies extending to the deep margin and 90 patients whose original biopsy specimen could not be obtained for review. In the remaining 211 patients, we obtained the original histological slides and/or paraffin blocks of their primary cutaneous melanomas. The melanomas were all re-examined by one pathologist (TMM) who did not have knowledge of the clinical course in any of these patients. The surgical procedures were performed by two surgeons (WAM and CMB) for 86% of these patients. The primary melanoma was widely excised with a 4–5 cm margin, except where interdicted by anatomical barriers, such as on the face. Therapeutic node dissections were performed for all patients with suspicious nodal metastases (clinical Stage II). In patients with apparent normal regional nodes (clinical Stage I), the decision regarding elective lymphadenectomy vacillated during the years reflecting a changing concensus of national opinion regarding its efficacy; the histopathological staging did not influence this decision until recent years.

Records from melanoma patients were reviewed and the data recorded on standardized forms designed for computer analysis. Follow-up data was obtained from patient records and by telephone interviews with the patients, their families or their primary physicians.

Microstaging

Level of invasion (Clark's method). The primary melanomas were categorized according to Clark's classification (6) into Level II (into papillary dermis), Level III (through papillary dermis at interface with reticular dermis), Level IV (into reticular dermis) and Level V (into subcutaneous tissues). A polarizing light source in the microscope greatly enhanced the visual identification of thick collagen fibers in the reticular dermis. This enabled us to better discriminate Level III from Level IV lesions.

Tumor thickness (Breslow's method). The vertical dimension of each melanoma was measured from the top of the granular layer to the base of the tumor using an ocular micrometer.[3,4] In ulcerated lesions, the thickness was recorded from the base of the ulcer to the base of the tumor. In cases where the distance from the top of the granular layer to the base of the tumor was greater than the distance from the ulcer to the base, the larger value was recorded.

Definition of Pathological Terms

Growth pattern. Melanomas were classified by microscopic analysis into lentigo maligna, superficial spreading and nodular types as defined by Clark.[5] In addition, we separately classified the growth pattern of 28 melanomas as polypoid. These lesions had an exophytic pattern with more of their vertical growth located above the epidermis than into the dermis. The edges of these polypoid lesions were typically everted with the lateral margin extending above the epidermis.

Ulceration. Ulceration was defined as an interruption of the surface epithelium involved by the tumor.

Lymphocyte infiltration. This was categorized into three grades. Grade I was absent to mild lymphocytic infiltration around lesions, showing very few or small groups of lymphocytes at their periphery. Grade II was moderate lymphocytic infiltration represented by multiple foci of lymphocytes at the edge and beneath the lesion. Grade III represented a marked lymphocytic infiltration where the lymphocytes were confluent occasionally forming bandlike features.

Pigmentation. Pigmentation was present if melanoma cells and/or macrophages contained melanin pigment in their cytoplasm. Lesions were scored as depigmented if virtually all cells had no cytoplasmic melanin.

Regression. The criteria set forth by Smith were followed.[23] Signs of regression were recognized whenever there was increased vascularity with scattered melanin-laden macrophages in the dermis and signs of fibrosis. Typically the overlying epidermis in the area of regression lacked melanin pigment while pigment was recognized in normal epidermis.

Statistics

The UAB Melanoma Registry is an ongoing retrospective/prospective analysis of all patients with malignant melanoma treated at the University of Alabama Medical Center. Detailed clinical and pathological information was computerized to facilitate data management and statistical analysis. Survival curves were calculated based upon the method of Kaplan and Meier.[14] A generalized Wilcoxon test[11] was used to determine if significant differences existed between curves. Chi-square tests were also employed in statistical assessments where appropriate. In addition, the multiple logistic regression procedure proposed by Cox[8] was used in a multifactorial analysis of prognostic factors.

Actuarial survival curves were calculated from patients who died with known melanoma; those who died without evidence of disease were computed as alive without disease for the time interval from treatment to death. In this report, survival curves are drawn as solid lines to the point of longest survival prior to death from disease; the continued broken lines indicate the survival duration of patients remaining alive.

Results

Level of Melanoma Invasion (Clark)

The data base for patients analyzed by Clark's microstaging method is shown in Table 1. Increasing level of invasion correlated inversely with survival and with the presenting pathological stage of disease. The cumulative incidence curves (Fig. 1) demonstrates that virtually all Level II lesions had vertical dimensions less than 1.5 mm while all Level V lesions exceeded 1.5 mm in thickness. Level III and IV lesions were more diverse in their vertical growth.

The median thickness for Clark's II lesions was 0.6 mm (range 0.2–3.2 mm). The thickest lesion in this group was a polypoid melanoma. Level III lesions had a median thickness of 1.4 mm (range 0.5–8.0 mm) Level IV lesions had a median thickness of 2.8 mm (range 0.6–12.6 mm), 22% of these were less than 1.5 mm in thickness (Fig. 1). Level V lesions had a median thickness of 5.1 mm (range 2.1–25.0 mm); all measured more than 1.5 mm, while 65% were greater than 4 mm.

TABLE 1. *Data Base Using Level of Invasion (Clark) Microstaging*

	II	III	IV	V	Total (#)
Number of patients	36 (17%)	70 (34%)	75 (36%)	28 (13%)	209
A. Presenting pathological					
Stage I	35 (20%)	62 (36%)	60 (35%)	15 (9%)	172
Stage II	1 (3%)	7 (21%)	14 (41%)	12 (35%)	34
					$p = 0.003$*
B. Thickness					
<0.76 mm	27 (65%)	12 (28%)	3 (7%)	0 (0%)	42
0.76–1.49 mm	7 (16%)	23 (51%)	15 (33%)	0 (0%)	45
1.50–4.00 mm	2 (3%)	30 (39%)	35 (46%)	9 (12%)	76
>4.00 mm	0 (0%)	5 (11%)	20 (45%)	19 (43%)	44
					$p < 0.0001$
C. Growth pattern					
Lentigo maligna	4 (50%)	3 (38%)	1 (12%)	0 (0%)	8
Superficial spreading	19 (46%)	13 (32%)	8 (20%)	1 (2%)	41
Nodular	12 (9%)	47 (37%)	44 (35%)	24 (19%)	127
Polypoid	1 (4%)	7 (25%)	17 (61%)	3 (10%)	28
					$p < 0.0001$
D. Melanoma ulceration					
Absent	27 (25%)	43 (40%)	29 (27%)	8 (8%)	107
Present	3 (4%)	25 (30%)	38 (46%)	17 (20%)	83
					$p < 0.0001$
E. Pigmentation					
Absent	2 (7%)	9 (30%)	15 (50%)	4 (13%)	30
Present	32 (19%)	58 (35%)	53 (32%)	23 (14%)	166
					$p = 0.172$
F. Lymphocyte infiltration around primary					
Grade I	19 (13%)	46 (31%)	63 (42%)	22 (14%)	150
Grade II and III	14 (36%)	18 (46%)	5 (13%)	2 (5%)	39
					$p = 0.171$

* p values represent the statistical significance levels correlating level of invasion and each pathological parameter.

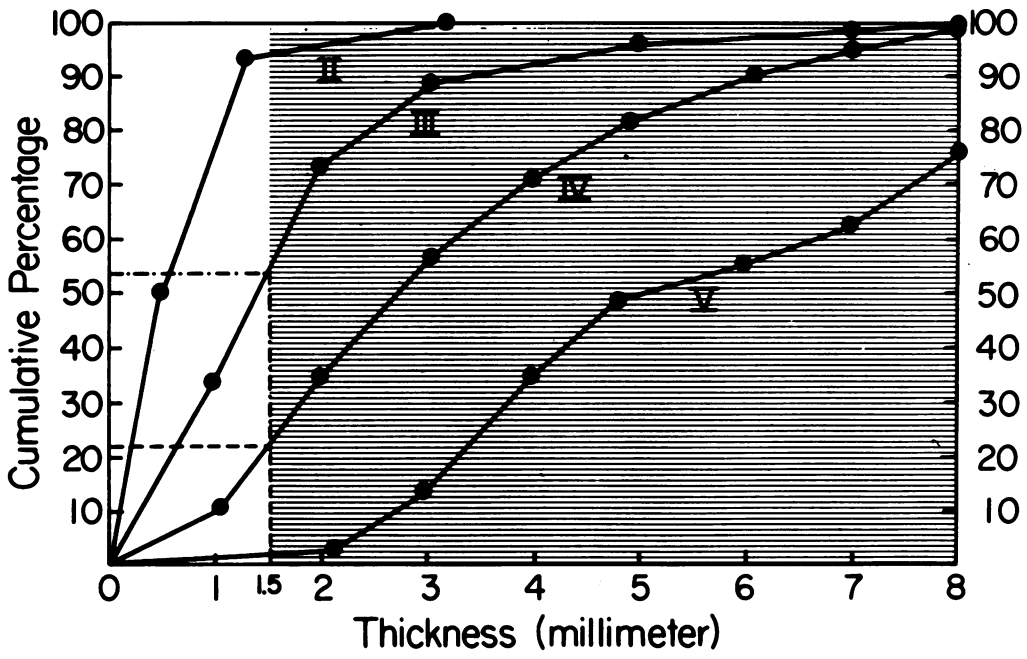

FIG. 1. Cumulative distribution of thickness measurements for each level of invasion (Clark's microstaging). As an example, 53% of Level III and 22% of Level IV melanomas had a thickness less than 1.5 mm (unshaded area).

Actuarial survival curves (Fig. 2A) show significant differences among all Clark's levels except Level II and Level III, which however, comprise 51% of the total patient population. Patients presenting with confirmed nodal metastases (pathological Stage II) had primary melanomas with twice the average thickness for each Clark's levels, compared with melanomas from patients with pathological Stage I disease. However, the Clark's level of invasion did not correlate with survival in patients presenting with pathologic Stage II disease. The number of pathological metastatic nodes and other parameters were overriding factors determining survival.

Melanoma Thickness (Breslow)

The data base for melanomas analyzed by Breslow's microstaging method is listed in Table 2. Numerous sets of measured thickness were examined for prognostic value (*e.g.*<1 mm, 1–4 mm, >4 mm), but none were found to have more discriminating value than those advocated by Breslow with one exception. For thicker lesions, we found more significant survival differences using 4 mm rather than 3 mm as demonstrated by actuarial survival curves (Fig. 2B). Three risk categories were identified. Patients with *thin melanomas* measuring 0.75 mm or less had localized disease. The only patient with pathological Stage II melanoma and a thin lesion was untreated for a year after misinterpretation of the biopsy, which was made correctly in retrospect when the patient subsequently presented with nodal metastases. Since our analysis was based primarily on re-examination of representative sections through the lesion rather than serial sectioning of the entire melanoma, it is possible that thicker areas may have existed in this specimen. Patients with *intermediate thickness melanomas* measuring 0.76–3.99 mm had increasing risk (up to 80%) of harboring regional and/or distant disease. Patients with *thick lesions*, exceeding 4 mm in thickness, had a very high risk (80%) of harboring distant metastatic disease, despite the fact that most had clinically undetectable metastatic disease at their initial presentation. Only one of 14 patients in this latter group survived more than five years. Patients presenting with pathological Stage II disease had thicker lesions than their Stage I counterparts (median thickness of 4.6 vs 1.6 mm respectively).

Comparison of Level vs Thickness as Prognostic Indicators

Figure 3A compares each level of invasion subdivided by thickness using actuarial calculations of five year survival rates. Within each level, there were gradations of thickness that influenced survival. For example, Clark's Level IV lesions measuring 0.76–1.49 mm had a 76% five year survival while thicker lesions (≥4.0 mm) had a 25% five year survival ($p = 0.02$). Similar discordance in five year survival figures was observed for each of the levels when subgrouped by thickness. Converse relationships were not observed when analyzing the sets of melanoma thickness subdivided by levels of invasion (Fig. 3B). For example, the five year survival for lesions measuring 1.50–3.99 mm was not significantly different for Level III, IV, and V lesions. To confirm these observations, we pooled the data from our clinical Stage I patients with that published by Breslow.[3] Within each Clark's level,

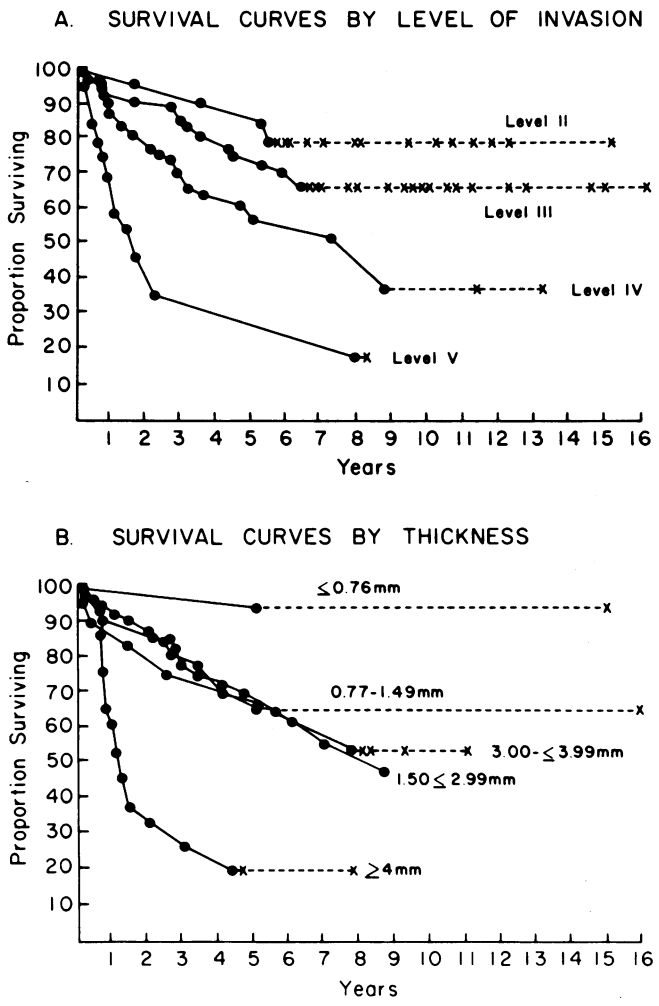

FIG. 2. Actuarial survival curves derived from microstaging. A) Clark's levels of invasion. The statistical differences between these levels were: II vs III ($p = 0.21$), III vs IV ($p = 0.07$), IV vs V ($p = 0.002$). B) Melanoma thickness. The statistical differences were: 0.76 vs 0.77–1.49 mm ($p = 0.006$), 0.77–1.49 vs 1.50–2.99 mm ($p = 0.84$) and 3.00–3.99 vs ≥ 4.0 mm ($p = 0.01$).

there were subgroups of different thickness with statistically significant differences in five year determinate disease-free rates (Table 3). However, within each thickness group, there were no subgroups of different Clark's level that influenced this rate significantly.

Growth Pattern

Survival curves for each of the 4 growth patterns of melanoma are shown in Figure 4A. Superficial spreading and lentigo maligna lesions had the best survival while polypoid lesions had the worst prognosis. The only statistically significant difference among these groups was between superficial spreading and polypoid lesions ($p = 0.001$).

Nodular melanomas with radial growth less than three rete pegs from the tumor constituted the majority (62%) of patients in our series. It is possible that some of these lesions may have been late superficial spreading melanomas with more lateral growth in unsampled sections of the slides. The median thickness for these lesions was 2.0 mm (1.5 mm for pathological Stage I disease, 4.4 mm for pathological Stage II). The majority (64%) had a thickness exceeding 1.5 mm while 72% were Clark's Level III or IV lesions (Tables 1 and 2). Five year survival in this group was 65%. There was no predeliction of nodular melanomas to any particular location on the body.

Patients with superficial spreading melanomas constituted 20% of the melanomas in our series. The median thickness for these lesions was 0.8 mm. A minority (24%) of patients had lesions exceeding 1.5 mm (Fig. 5). Almost half of the melanomas in this group were Level II lesions. Five year survival was 73%. The three deaths were all Clark's Level III lesions. Two of the three had lesions exceeding 1.5 mm.

Polypoid melanomas were the worse group prognostically. These constituted 13% of the total group. Their median thickness was 4.8 mm (3.6 mm for Stage I disease, 6.3 mm for Stage II disease). All lesions measured greater than 1.5 mm; 61% in fact measured greater than 4 mm (Fig. 5). The majority (61%) of these lesions were Clark's Level IV. Five year survival for the group was 47%.

There were 8 patients (4%) with lentigo maligna lesions. The median thickness was 0.6 mm. All patients presented with pathological Stage I disease. The five year survival was 71%. Both patients who died with metastatic disease had lesions exceeding 1.77 mm thickness.

Lymphocyte Infiltration

For patients with pathological Stage I disease, there was an inverse correlation with thickness and the magnitude of lymphocyte infiltrate around the primary melanoma lesion ($p = 0.003$). Patients with absent to minimal lymphocyte infiltration had a median 2.3 mm thickness, while those with a heavy lymphocyte infiltration had a median 1.1 mm thickness. There was no correlation of lymphocyte infiltration and thickness for patients with pathological Stage II disease. Grade II or III lymphocyte infiltration surrounding the melanomas was observed in 100% of patients with lentigo maligna lesions, 90% of those with superficial spreading melanoma and 60% of nodular melanomas. However, these differences among different grades of lymphocyte infiltration and thickness did not influence survival significantly (Fig. 4B).

Ulceration

The presence of ulceration on the microscopic sections of melanomas was a significant adverse determi-

nant of survival (Fig. 4C). Patients with ulceration (42% of total group) had a five year survival rate of 52% while those without ulceration had a 77% five year survival rate ($p = 0.001$). There was a positive correlation of ulceration with thickness ($p < 0.0001$). The median thickness for patients with ulceration was 3 mm while those without ulceration had a median thickness of 1.3 mm. Lesions thicker than 1.5 mm were associated with an 80% incidence of ulceration. Likewise, more than 66% of patients with Clark's Level IV or V lesions had ulcerations (Table 1).

Pigmentation

Although only 18% of melanomas had evidence of depigmentation, this was also a significant adverse determinant of survival (Fig. 4D). Five year survival rate of patients without lesion pigmentation was 36% while those patients with pigmentation had a 69% five year survival rate ($p = 0.006$). Lack of pigmentation occurred more frequently in thicker lesions (Table 2, $p = 0.05$).

Regression

Only a small minority (17/170 patients) had evidence of lesion regression. This factor had no significant influence on survival ($p = 0.13$).

Age, Sex and Location

There was no significant correlation of age with histopathological features of melanoma. There was a trend for patients in the sixth and seventh decades, of life to have somewhat thicker lesions.

Melanomas in our series were almost equally divided between males and females. Females had a slightly better survival rate than males, although this was not a statistically significant difference when examined as a single parameter ($p = 0.479$). Lower leg lesions occurred predominantly in females (79%) while the majority of trunk lesions were in males (70%).

There were several histopathological features which correlated with location of the lesion. First, all lentigo maligna lesions were located on the face. Second, survival rates for trunk lesions were worse than lesions of head and neck, lower extremity or upper extremity. These differences were not statistically significant when analyzed as single parameters ($p = 0.354$).

Multifactorial Analysis

Prognostic factors analyzed for their influence on survival were: lesion thickness, Clark's level of invasion, ulceration, pigmentation, lymphocyte infiltration, growth pattern, regression, primary lesion sites, pathological and clinical stages, surgical treatment, age and

TABLE 2. *Data Base Using Tumor Thickness (Breslow) Microstaging*

	<0.76 mm	0.76–1.49 mm	1.50–3.99 mm	≥4 mm	Total (#)
Number of patients	42 (20%)	47 (23%)	78 (36%)	44 (21%)	211
A. Presenting pathological					
Stage I	41 (24%)	43 (25%)	66 (38%)	24 (13%)	174
Stage II	1 (3%)	2 (6%)	11 (32%)	20 (59%)	34
					$p < 0.0001$*
B. Level of invasion					
Level II	27 (73%)	7 (19%)	2 (8%)	0 (0%)	36
Level III	12 (17%)	23 (33%)	30 (43%)	5 (7%)	70
Level IV	3 (4%)	15 (21%)	35 (48%)	20 (27%)	73
Level V	0 (0%)	0 (0%)	9 (32%)	19 (68%)	28
					$p < 0.0001$
C. Growth pattern					
Lentigo maligna	4 (50%)	2 (25%)	2 (25%)	0 (0%)	8
Superficial spreading	24 (57%)	8 (19%)	9 (21%)	1 (3%)	42
Nodular	14 (11%)	32 (25%)	55 (43%)	26 (21%)	127
Polypoid	0 (0%)	0 (0%)	11 (39%)	17 (61%)	28
					$p < 0.001$
D. Ulceration					
Absent	32 (30%)	29 (27%)	38 (35%)	9 (8%)	108
Present	4 (5%)	12 (15%)	34 (41%)	32 (39%)	82
					$p < 0.0001$
E. Pigmentation					
Absent	2 (6%)	5 (16%)	13 (42%)	11 (36%)	31
Present	38 (23%)	37 (22%)	61 (37%)	30 (18%)	166
					$p = 0.051$
F. Lymphocyte infiltration					
Grade I	24 (16%)	29 (19%)	58 (39%)	40 (26%)	151
Grade II and III	14 (37%)	13 (34%)	9 (24%)	2 (5%)	38
					$p = 0.003$

* p values represent the statistical significance levels correlating tumor thickness and each pathological parameter.

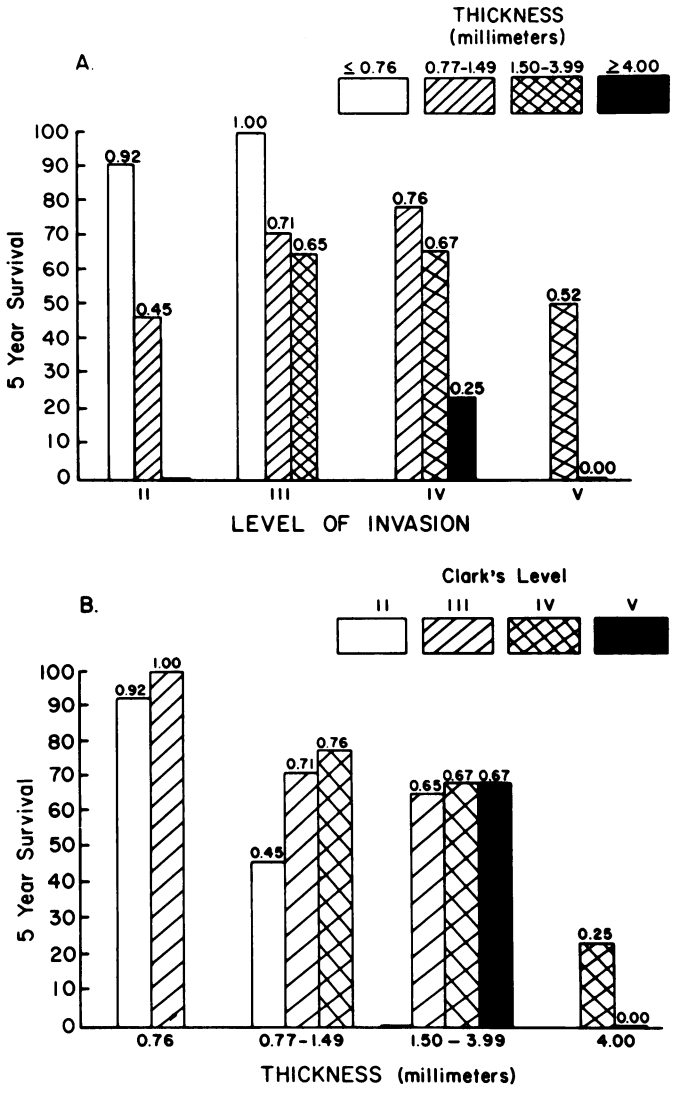

FIG. 3. Comparison of two microstaging methods: A) Levels of invasion subgrouped by thickness. There were statistically significant differences among thickness groups within each level of invasion. B) Thickness subgrouped by level of invasion. There were no statistically significant differences among the levels of invasion within each thickness group.

sex. Table 4 presents the relative importance of each single factor unadjusted for other factors. For example, the thickness of melanoma was highly predictive of five year survival (p = <0.00001) while the alternative surgical treatments (wide excision ± elective lymphadenectomy) did not influence survival (p = 0.638). A multifactorial analysis was then performed to examine the primary predictor factors that independently correlated with five year survival, while simultaneously accounting for the contribution of the other factors listed above. Each variable was analyzed in sequence for their additive prognostic value after the preceding factors had been accounted for. For example, when level of invasion was ranked in the first position followed by tumor thickness, the p values for each variable were 0.003 and 0.001 respectively. This indicated that the parameter of tumor thickness contributed additional prognostic information after level of invasion had been accounted for. On the other hand, when these variables were arranged in reverse order, thickness was a highly predictive factor (p = 0.0002), but level of invasion had no additional predictive influence after thickness was accounted for (p = 0.7105).

The influence of these factors on survival was examined using a cohort of 97 patients who survived more than five years. Based upon the model proposed by Cox,[8] a statistical (forward) selection procedure selected a subset of factors that was most predictive of five year survival. The subset consisted of the following five prognostic indicators (Table 5): pathological stage (p = 0.0014), lesion ulceration (p = 0.006), surgical treatment (p = 0.024), thickness (p = 0.032), and primary lesion site (p = 0.038). Each factor was adjusted for all other factors under analysis. Although several variables, such as clinical stage, Clark's level, pigmentation, and age were significant as single factor predictors (Table 4), they were excluded from the subset as secondary variables. On the other hand, surgical treatment and primary lesion site became significant prognostic variables after adjusting for other factors.

This statistical analysis enabled us to derive an equation (incorporating the factors in the selected subset) for predicting an individual patient's five year survival: $\log [\theta/(1 - \theta)] = 0.36969 - 2.38932P + 0.01917U + 1.60759T - 0.44481D + 1.83750S$, where θ = the probability of five year survival, P = pathological stage, U = ulceration, T = treatment, D = depth of invasion, and S = primary lesion site. The equation predicted an individual patient's probability of five year survival in close agreement with the observed numbers of five year survivals (Table 6). The close fit between the mathematical model and observed survival, and the discordance of factors found significant in the two types of statistical analysis strongly supports the superiority of regression analysis as a technique for more accurately identifying important prognostic variables.

Discussion

A multifactorial analysis is a powerful statistical method that minimizes selection bias, permits a more sophisticated examination of clinicopathologic correlates, and discriminates those factors that independently influence survival rates. Mathematical approaches such as this have been previously advocated to select different therapeutic strategies, such as selecting alternative surgical treatments and for identifying high risk patients as potential candidates for adjunctive

TABLE 3. *Melanoma Microstaging Five Year Disease-free Rate*§

Level of Invasion	Thickness (mm) 0–0.75	0.76–1.49	1.5–2.25	2.26–3.0	>3.0	Total
II	100% (55)*	69% (13)*				94% (68)
III	100% (16)†	65% (23)†	69% (13)	50% (8)	33% (5)	71% (65)
IV		66% (9)	68% (19)‡	11% (9)‡	25% (20)	43% (57)
V				100% (2)	15% (13)	27% (15)
Total	100% (71)	66% (45)	69% (32)	37% (19)	23% (38)	

§ The 205 patients at risk for recurrence five years or longer represent combined statistics from the University of Alabama Melanoma Registry and a previously published series[3] from the George Washington Medical Center. *p = 0.00002; †p = 0.008; ‡p = 0.005.

therapy trials.[7,20] Of the 13 variables compared simultaneously from our data, only five factors independently influenced survival of the entire population of melanoma patients: pathological stage, thickness, lesion ulceration, surgical treatment and anatomical location.

The pathological stage of disease was the most significant determinant of survival, as it reflected the localized, regionalized or distant extent of disease. The measured thickness of the primary melanoma was also an independent variable. It was the most important determinant of survival for Stage I patients, but had less predictive value for patients presenting with pathological Stage II and III disease. A multivariate analysis of 118 patients treated at the National Institutes of Health also showed that the number of metastatic regional nodes was the most important prognostic factor in pathologic Stage II disease and that the micro-

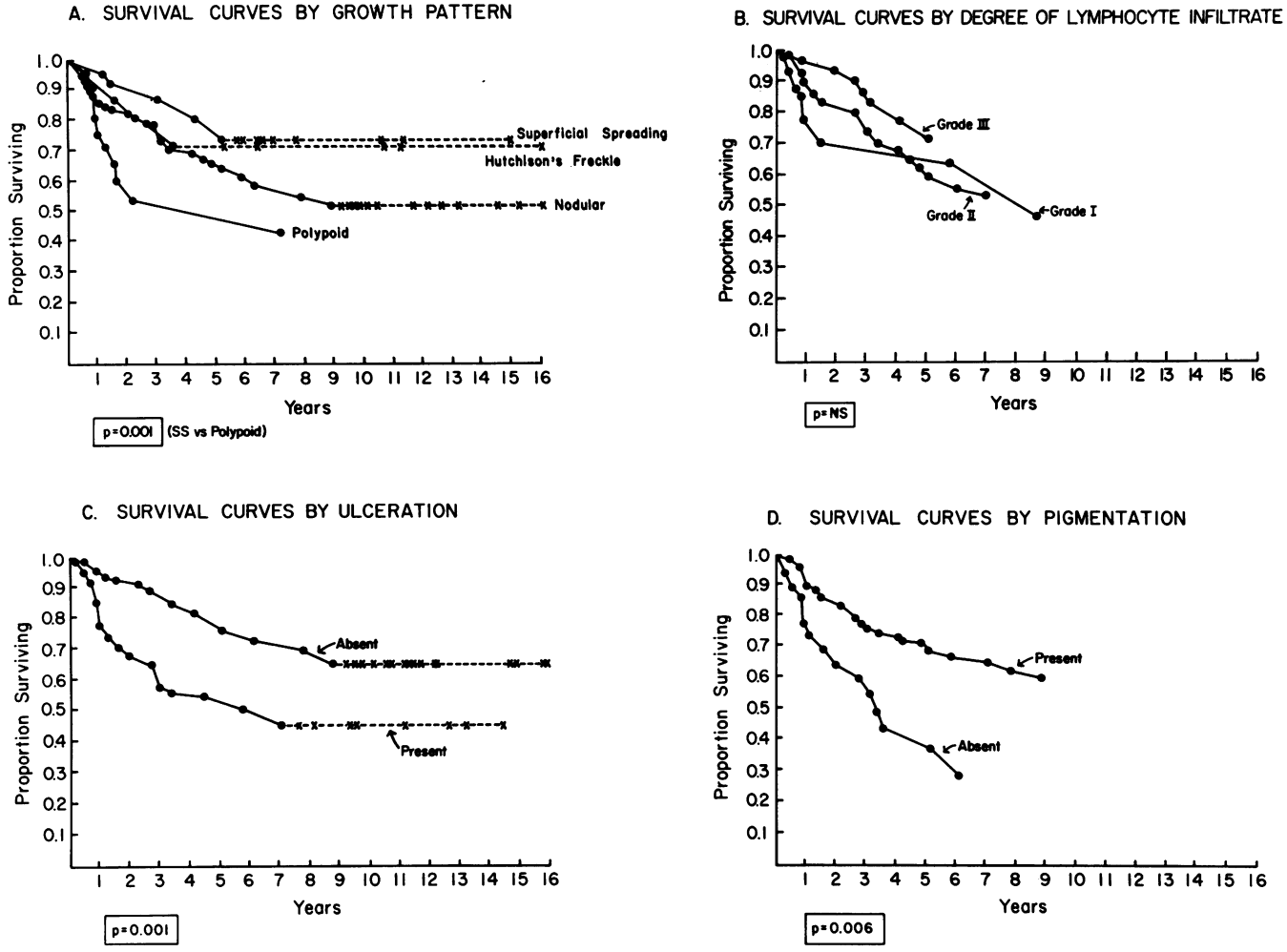

FIG. 4. Actuarial survival curves for four histopathological parameters of cutaneous melanoma.

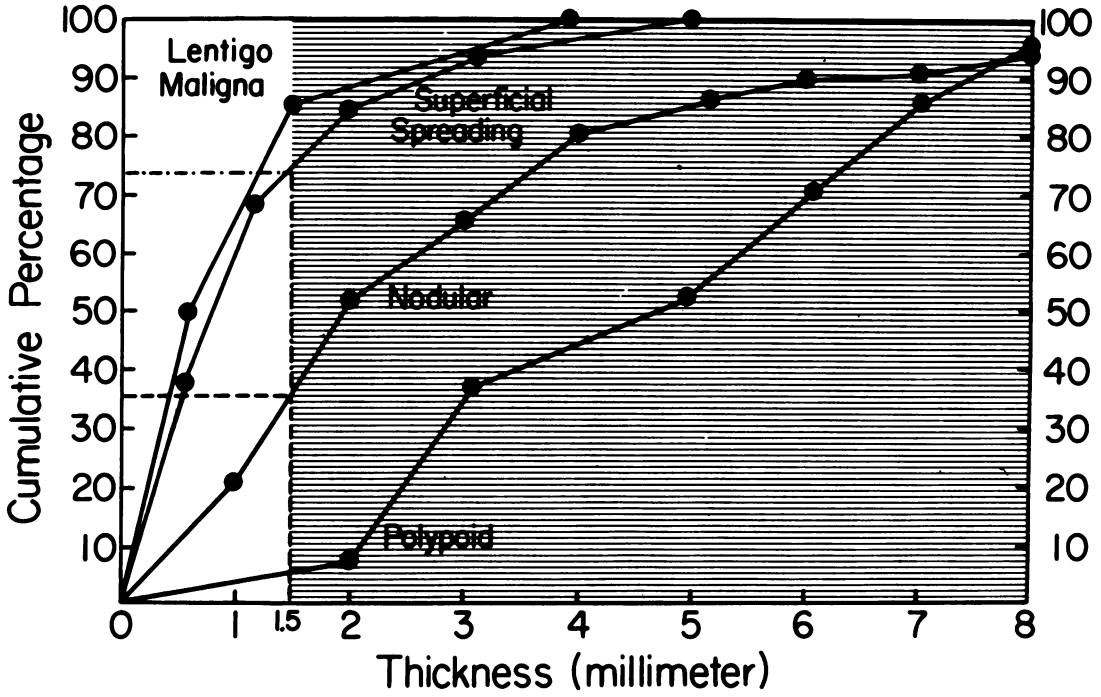

FIG. 5. Cumulative distribution of thickness measurements for each growth pattern.

staging of the primary melanoma was of prognostic importance only in patients with histologically negative nodes.[7]

In selecting optimal treatment alternatives for clinical Stage I melanoma patients, the measured thickness of melanoma invasion may be a valuable guide for identifying patients at risk for local, regional or distant disease. Thin melanomas with vertical dimensions less than 0.76 mm are localized in almost all cases, a finding that has been well documented in virtually all reported series. There is, therefore, no need for elective regional lymphadenectomy or systemic adjunctive therapies for such patients. Intermediate thickness lesions measuring between 0.76 and 4.0 mm have an increasing risk of harboring microscopic regional disease in draining lymph nodes, thus forming the rationale for performing elective regional lymphadenectomy in clinical Stage I patients. An improved survival rate with lymphadenectomy and a strong correlation of increasing melanoma thickness with greater risk of regional metastases has been well demonstrated in several series.[3,4,7,12,13,26] In our series, patients with melanoma of intermediate thickness (0.76–3.99 mm) had a statistically increased survival rate after elective node dissection, compared to those patients who had excision of the primary melanoma and subsequent lymphadenectomy for clinically apparent disease.[2] However, preliminary results of two randomized trials of elective lymphadenectomy for extremity melanomas have not demonstrated a statistically significant benefit after five years of follow-up.[21,25] Their results may become significant with a longer follow-up interval, since in our series the influence of lymphadenectomy was greatest at eight years or longer after surgery. Moreover, differences in study design and patient population between our study and the two randomized trials preclude any final judgment regarding the efficacy of elective lymphadenectomy but it appears from our data that there are subgroups of melanoma patients that benefit from this procedure.[2]

TABLE 4. *Single Factor Analysis of Melanoma (Single Variables Affecting Five Year Survival Rate Unaccounted for by Other Variables)*

Variables	p
Thickness	<0.00001
Pathological stage	0.00002
Clinical stage	0.0002
Clark's level	0.003
Ulceration	0.003
Pigmentation	0.025
Age	0.053
Growth pattern	0.231
Primary lesion site	0.354
Lymphocyte infiltration	0.438
Sex	0.479
Regression	0.590
Surgical treatment	0.638

The third risk category identified in our series was patients with thick melanomas exceeding 4 mm. These patients were at very high risk for harboring microscopic (or subclinical) distant metastatic disease at the time of initial diagnosis. The five year survival of 20% for patients with melanomas >4 mm in our series

contrasts with that from the World Health Organization Melanoma Center whose patients with lesions exceeding 4.6 mm had a 50% or greater five year survival.[25] Their study, however, was restricted to extremity melanomas in a predominantly female population, while ours included all body sites, an equal number of males and females and a greater proportion of nodular melanomas, again stressing the need for multifactorial analysis in interpreting results.

Melanomas located on the upper extremity had a statistically better survival rate than melanomas in other locations. Trunk lesions had the worst prognosis of the four major groups analyzed, but this was not statistically significant. Most series have similarly reported that extremity melanomas fare better than trunk lesions.[7,15,22,24,31] The majority (79%) of our patients with extremity melanomas were females, whereas the majority (70%) of patients with trunk lesions were males. However, location, not sex was identified as the more important variable. The location of melanoma is thus an important factor to account for by stratification in clinical trials. Differences among clinical studies comparing alternative surgical treatments for clinical Stage I melanoma patients may have been significantly influenced by the mix of different melanoma thicknesses and anatomic locations between different treatment groups.

The presence of lesion ulceration as determined by microscopic evaluation correlated strongly with melanoma thickness (Table 2, $p = 0.0001$). Despite this, ulceration was an independent variable delineated by the multifactorial analysis. Thus, ulceration influenced survival within stage of disease (I vs II), thickness groups and types of surgical treatment.

The Clark's level of invasion significantly correlated with survival in the single factor analysis. However, the multifactorial analysis did not identify it as an independent variable. Its predictive value appeared generally to correlate with lesion thickness. However, there was some discordance that lessened its prognostic value. For example, patients with thicker Level II lesions, such as exophytic polypoid melanomas, generally fared poorly while those with thinner Level IV lesions had a relatively good prognosis especially when compared to survival associated with thicker Level IV lesions. Breslow[3] and Wanebo[26] have previously pointed out that tumor thickness and Clark's levels were congruent for Levels II and V, but not for Levels III and IV where there was wide variations in thickness and survival rates. Our data is exactly consonant with this view. On the other hand, survival rates for different thickness categories were unchanged when subgrouped by Clark's levels. These relationships were the same for our own analysis and from pooled data with Breslow's series (Table 3). Thus, it appears that the actual histological structures invaded by the melanoma are less predictive than the measured thickness. Moreover, others have reported that a microstaging technique using tumor thickness was easier than making assignments of Clark's level and was therefore more reproducible.[7,26]

Other pathological factors also seemed to derive their prognostic value from the thickness of the primary melanoma. For example, lentigo maligna lesions on the face are generally regarded as highly curable melanomas. In our series, patients were cured if their lentigo maligna lesions were thin, but death occurred in two out of three patients with such melanomas of intermediate thickness. Polypoid melanomas were associated with a very poor prognosis but this association was also accounted for by their extreme thickness. Depigmentation was an adverse determinant of survival, but this was a secondary variable that correlated with thickness. Lymphocyte infiltration was not clearly associated with improved survival rate in this study despite the fact that thicker lesions were associated with a diminished host response. There was no correlation of survival with lesion regression in our series.

Microstaging using tumor thickness is thus an important factor for determining prognosis and guiding initial management of melanoma patients. It should be a critical aspect in any analysis of clinical trials concerning surgical treatment alternatives and adjunc-

TABLE 5. *Multifactorial Analysis of Melanoma (Dominant Variables Affecting Five Year Survival Rate after All Other Variables Have Been Accounted For)*

Variables	p
Pathological stage (I, II)	0.0014
Lesion ulceration	0.006
Surgical treatment	0.024
Thickness	0.032
Primary lesion site (upper extremity vs other)	0.038

TABLE 6. *Observed and Predicted Five Year Survivals From Logistic Regression Equation*

Predicted Probability of Five Year Survival	Total No. of Patients	No. of Five Year Survivals	
		Observed	Predicted
0–19%	18	1	1.4
20–39%	7	2	2.2
40–59%	11	7	5.7
60–79%	19	13	13.6
80–100%	42	38	38.1
Total	97	61	61.0

tive therapies. Our data distinguishes three subgroups of melanomas and relates the vertical dimension of their growth to subsequent biologic behavior. Thick melanomas (≥4.0 mm) were the most aggressive lesions. Pathologically, these lesions were associated with an increased incidence of ulceration, depigmentation and a diminished infiltration by host lymphocytes. Clinically, they were associated with a high risk of distant metastases. Converse relationships were observed for melanomas less than <0.76 mm in thickness. It is not clear biologically why melanoma thickness alone is a significant prognostic variable, especially when considering wide variations of skin thickness in different anatomic locations. Thicker lesions may represent more advanced melanomas and reflect an inherent biological aggressiveness of lesions with vertical growth as opposed to radial growth.[5]

The histopathological staging of melanomas provides important data relevant to clinical management. It, therefore, behooves the surgeon to consider carefully his biopsy techniques for suspicious pigmented lesions of the skin. Shave or curretted biopsies are contraindicated because they do not remove the entire lesion and thus compromise the accuracy of microstaging. An excisional or a punch biopsy that extends to the underlying subcutaneous tissues is essential.

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