Risk Assessment in Localized Primary Cutaneous Melanoma

A Southwest Oncology Group Study Evaluating Nine Factors and a Test of the Clark Logistic Regression Prediction Model

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Abstract

*We studied 9 clinical and pathologic factors in 259 patients using Cox model regression analysis to determine which factors have independent predictive value. Median follow-up time in all patients still alive was 12.3 years (range, 1.7 to 16.7 years). Tumor-infiltrating lymphocytes (*P = *.005), primary site (*P = *.006), and thickness (*P = *.02) had independent predictive value. Ulceration (*P = *.06) and age (*P = *.07) had marginal value. We used 6 of those factors to test the Clark logistic regression prediction model, which accurately predicted 8-year survival in 121 (72.9%) of 166 patients and accurately predicted melanoma-specific mortality in 32 (43%) of 74 patients. The combined or overall accuracy of the Clark model was only 64%.*

Multiple factors in addition to tumor thickness may be useful for assessing prognosis in cutaneous melanoma. In 1989, Clark and coinvestigators[1] published a logistic regression prediction model based on tumor progression and the use of 6 clinical and pathologic factors. Tumor progression is in part the concept of a melanoma changing from the radial growth phase to the vertical growth phase. They derived the model from a study of 386 patients, of whom 122 had tumors in the radial growth phase and 264 had tumors in the vertical growth phase. Of the patients with radial growth phase tumors, 100.0% survived 8 years, whereas survival for patients with vertical growth phase tumors was only 71.2%. Logistic regression analysis, both univariate and multivariate, was used to evaluate the various factors in the 264 patients with tumors in the vertical growth phase to produce a prediction model.

The model was presented in 2 ways: as a mathematical formula and in tabular form. The tabular form consists of 2 tables that can be used by clinicians and pathologists without requiring a computer. Clark and coworkers[1] validated the model using a separate group of patients from their clinic. The tables have been widely published in journal articles and textbooks.[2,3] Although there have been a few attempts to validate the model using patients from different geographic locations, the studies have limited numbers of patients.[4-6]

The Melanoma Committee of the Southwest Oncology Group (SWOG) is actively involved in evaluating new and different therapeutic regimens for patients with malignant melanoma. Some of those studies include patients with localized cutaneous melanoma with a significant risk of recurrence and metastasis.[7,8] It is always important to devise studies in which the patients have comparable risk when

placed into 2 or more arms of a study. Tumor thickness is the dominant single factor in assessing risk of individual patients.[9,10] Other factors seem to have a part in the biology of malignant melanoma.[1,10] It is tempting to speculate that a model using multiple factors such as those provided by Clark and coworkers[1] might refine our ability to design and evaluate therapeutic trials. This also may apply to trials that include sentinel lymph node examination. However, the Clark model needs validation using a large group of patients from a different patient population and setting.[11,12]

To validate the Clark model with a new population of patients, we used data from a previously reported SWOG study (SWOG-8049) of vitamin A vs observation in patients with localized cutaneous melanoma.[13] That study showed that there was no benefit to the patients receiving vitamin A.

We also wanted to evaluate 9 factors that may be relevant to survival using the Cox proportional hazards regression analysis.[14] Logistic regression analysis and Cox regression analysis are different. Logistic regression analysis evaluates the relationship of 2 or more factors (continuous or discrete) to a binary outcome such as alive or dead at a given time point. Cox regression analysis uses more end point information because, in addition to being able to incorporate censored observations, it includes the duration of survival. In malignant neoplasms such as melanoma, long follow-up is essential to completely characterize survival.[10] In the present study, we analyzed multiple potential prognostic factors for survival by the Cox method in a data set with extensive follow-up.

Materials and Methods

A total of 386 patients were registered to SWOG-8049 between August 1981 and March 1987. Of 354 eligible patients, both the clinical and extensive pathology data were available for Cox regression modeling for 259 patients. In testing the Clark model, patients with a competing or unknown cause of death before 8 years were excluded, as were alive patients lost to follow-up (censored) before 8 years. All tumors were in the vertical growth phase and measured at least 0.76 mm in thickness. Median follow-up time among patients still alive was 12.3 years (range, 1.7-16.7 years).

Vertical growth phase was assigned to a case when the tumor cells in the dermis formed a rounded expansile tumor mass that was 15 to 25 cells wide and larger than any of the nests of tumor present in the overlying epidermis.[1,15] Tumor thickness was measured vertically from the granular layer of the epidermis to the deepest tumor cell in the vertical growth phase.[8] We used cut points of 1.50 and 4.00 mm, to match the American Joint Committee on Cancer (AJCC) TNM staging used at the time of analysis. Satellitosis was not used in obtaining the tumor thickness. Angiolymphatic spread was not measured unless in the immediate vicinity of the main vertical growth phase nodule. Mitoses were counted by surveying the entire vertical growth phase nodule for what appeared to be the most mitotically active area. One square millimeter was counted. If necessary to obtain a square millimeter, adjacent step sections that included vertical growth were examined.

Regression was identified when there was melanoderma but complete absence of atypical melanocytes in the epidermis and dermis. Fibrosis and new blood vessel formation were characteristically present as well. Tumor-infiltrating lymphocytes (TILs) were present when lymphocytes appeared to be directly related to the tumor cells in the vertical growth nodule.[1] The lymphocytes had to partially infiltrate the tumor nodule by surrounding tumor cells. Evidence of cell death was not required.

If lymphocytes were band-like and completely surrounded the nodule, they were assigned to the brisk category **Image 1**. If there was a defect in this band-like quality that was 0.30 mm or greater in dimension, the TILs were assigned to the nonbrisk category. If lymphocytes were present but only around vessels and not directly related to the tumor cells, TILs were assigned to the absent category.

Ulceration was identified when there was a defect in the overlying epidermis associated with fibrin deposition and inflammation. Lymph node dissection was coded as either yes or no, and sections of the lymph nodes following a dissection were included for examination along with the primary melanoma. If lymph node dissection was performed, all lymph nodes had to be negative for melanoma by routine

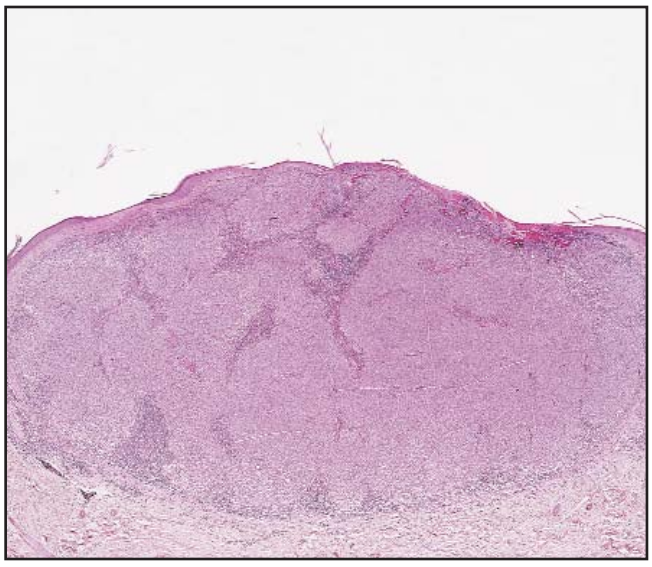

Image 1 The primary cutaneous melanoma of 1 of 30 patients coded as having "brisk tumor-infiltrating lymphocytes." The patient was alive and well at 10.5 years of follow-up (H&E, ×8.25).

histopathologic evaluation. No patient underwent sentinel lymph node biopsy, and neither serial sectioning nor immunohistochemical staining was used to evaluate lymph nodes for metastasis. Primary site was coded as extremities, trunk, or head and neck. Age was used as a continuous variable in the Cox regression analysis. For descriptive purposes, a cutoff of age 60 was used for survival estimates and frequency counts.

Cox Regression Analysis

Overall survival was analyzed using a multivariate Cox regression model[14] and was measured from the date of trial registration to the date of last contact or death. The 6 clinical and pathologic factors identified by Clark et al[1] as having independent predictive value were included. Those factors are sex, primary site (extremity vs trunk vs head and neck), tumor thickness (1.50 mm or less vs 1.51-4.00 mm vs >4.00 mm), histologic regression (yes or no), mitotic rate (0 vs 1-6 vs 7 or more), and TILs (absent or slight vs nonbrisk vs brisk). Three additional factors—age (continuous variable), ulceration (yes or no), and lymph node dissection (yes or no)—were included because they have been shown to be important predictors of survival in other studies.[1,10,16-19] The overall survival rates were estimated according to the method of Kaplan and Meier.[20] All statistical tests were 2-sided. All computing was performed using the SAS statistical package (STAT Software, version 6.07, SAS Institute, Cary, NC).

Testing the Clark Prediction Model

Clark et al[1] excluded the following patients from analysis: (1) those with a competing cause of death before 8 years and (2) alive patients lost to follow-up before 8 years. In testing the Clark prediction model, we also excluded these patients. We used the primary site categories of axial or subvolar vs extremity and tumor thickness categories of less than 1.70 mm vs 1.70 mm or more. In the article by Clark et al,[1] a prediction model was proposed as follows:

Probability alive at 8 years = $1/(1 + e^{-y})$

where

y = log odds of being alive at 8 years =
–3.07 + (1.07 if female, 0 if male)
+ (1.33 if primary site in the extremities, 0 if not)
+ (1.40 if tumor thickness <1.70, 0 if 1.70 or more)
+ (1.03 if histologic regression absent, 0 if present)
+ (2.46 if mitotic rate = 0, 1.25 if 0.1 to 6, 0 if >6)
+ (2.43 if brisk TILs, 1.26 if nonbrisk, 0 if absent)

A resulting probability of less than .5 was taken to indicate a failure (not living 8 or more years) and .5 or more a success.[1] To assess how well the Clark logistic model predicted 8-year survival, the particular factors for each of the 259 patients were entered into the model and a predicted 8-year survival probability was computed. Then, for each case, the predicted result was compared with the actual result.

Results

Table 1 shows the characteristics of the SWOG cohort. The median age was 46 years, and 24.7% of the patients were 60 years old or older. The majority of patients were male (57.1%). Primary tumors were generally located on the extremities (38.2%) or on the trunk (43.2%), and the majority were intermediate thickness (1.51-4.00 mm, 57.5%). Ulceration occurred in 33.6% of patients, lymph node dissection in 30.1% of patients, and histologic regression in 29.0% of patients. Only 6.6% of patients had no mitoses. The majority (58.7%) had between 1 and 6 mitoses. Only 30 patients (11.6%) had brisk TILs; the majority (50.6%) had absent or slight TILs.

Table 1
Patient Characteristics*

Characteristic	Entire SWOG Cohort (N = 259)	Portion of SWOG Cohort Used for Validating Clark Model (n = 240)
Age (y)		
Median	46	46
Range	16-86	16-86
<60	195 (75.3)	186 (77.5)
≥60	64 (24.7)	54 (22.5)
Sex		
Male	148 (57.1)	136 (56.7)
Female	111 (42.9)	104 (43.3)
Primary site		
Extremities	99 (38.2)	96 (40.0)
Trunk	112 (43.2)	—
Head and neck	48 (18.5)	—
Other	—	144 (60.0)
Tumor thickness (mm)	≤1.50: 75 (29.0) 1.51-4.00: 149 (57.5) >4.00: 35 (13.5)	<1.70: 82 (34.2) 1.70-3.60: 114 (47.5) >3.60: 44 (18.3)
Ulceration		
No	172 (66.4)	160 (66.7)
Yes	87 (33.6)	80 (33.3)
Lymph node dissection		
No	181 (69.9)	169 (70.4)
Yes	78 (30.1)	71 (29.6)
Histologic regression		
No	184 (71.0)	169 (70.4)
Yes	75 (29.0)	71 (29.6)
No. of mitoses		
0	17 (6.6)	16 (6.7)
1-6	152 (58.7)	143 (59.6)
≥7	90 (34.7)	81 (33.8)
Tumor-infiltrating lymphocytes		
Absent or slight	131 (50.6)	122 (50.8)
Nonbrisk	98 (37.8)	89 (37.1)
Brisk	30 (11.6)	29 (12.1)
Follow-up status		
Alive	146 (5.4)	140 (58.3)
Dead	113 (43.6)	100 (42.0)

* Data are given as number (percentage) unless otherwise indicated.

Table 2
Multivariate Risk Ratios of Time to Death from Cox Regression Model*

Factor	Risk Ratio (95% Confidence Interval)	*P*
Age†		.07
1-year increase	1.01 (0.99-1.04)	
10-year increase	1.13 (0.89-1.43)	
Sex		.89
Female	1.00	
Male	0.97 (0.66-1.44)	
Primary site		(.006)
Extremities	1.00	
Trunk	1.51 (0.94-2.41)	.09
Head and neck	2.35 (1.40-3.96)	.001
Tumor thickness (mm)		(.02)
≤1.50	1.00	
1.51-4.00	1.45 (0.87-2.42)	.16
>4.00	2.45 (1.29-4.65)	.006
Ulceration		.06
No	1.00	
Yes	1.45 (0.98-2.17)	
Lymph node dissection		.89
No	1.00	
Yes	0.97 (0.63-1.50)	
Histologic regression		.66
No	1.00	
Yes	1.10 (0.72-1.70)	
No. of mitoses		(.29)
0	1.00	
1-6	3.14 (0.75-13.08)	.12
≥7	3.02 (0.71-13.01)	.14
Tumor-infiltrating lymphocytes		(.005)
Brisk	1.00	
Nonbrisk	9.10 (2.19-37.80)	.002
Absent or slight	10.44 (2.53-43.07)	.001

* All risk ratios compared with the baseline category indicated by a risk ratio of 1.00. *P* values shown in parentheses are global *P* values for the variable.
† Age was analyzed as a continuous variable; the risk ratios shown correspond to increases of 1 year and 10 years.

Cox Regression Analysis

The effect of these factors on overall survival was analyzed in a multivariate Cox regression model. Results are shown in **Table 2**. TILs ($P = .005$), primary site ($P = .006$), and tumor thickness ($P = .02$) were all significant predictors of survival. Ulceration ($P = .06$) and age ($P = .07$) were marginally predictive of survival. Sex, lymph node dissection, histologic regression, and number of mitoses were not predictive of survival. We reran our model using thickness as a continuous variable to assess whether model results differed. There were no substantive changes in either the direction or statistical significance of the Cox regression coefficients (data not shown).

Figure 1, **Figure 2**, **Figure 3**, and **Table 3** show overall survival by each of the 3 factors found to be significant survival predictors in the multivariate model. Patients with a primary site in the extremities had marginally better survival than patients with a primary site in the trunk ($P = .09$) and better survival than patients with a primary site in the head and neck ($P = .001$). Patients with thin tumors (1.50 mm or less) had better survival than patients with thick tumors (>4.00 mm; $P = .006$). Patients with brisk TILs (Image 1) had better survival than patients with absent or slight TILs ($P = .001$) and patients with nonbrisk TILs ($P = .002$). Five- and 10-year survival estimates for all factors are shown in **Table 4**.

Testing the Clark Prediction Model

Thirteen patients had a competing cause of death (8 patients) or an unknown cause of death (5 patients) before 8 years of follow-up, and 6 patients were lost to follow-up before 8 years. These patients were excluded from this portion of the analysis, leaving 240 patients for validation of the Clark model. Actual 8-year survival by tumor thickness for the SWOG cohort is shown in **Table 5**. Also shown is the 8-year survival for the Clark cohort from which the logistic model was derived. Overall 8-year survival for the Clark cohort is similar to the SWOG cohort (71.2% vs 69.2%). Overall trends for both samples also are similar (decreasing likelihood of 8-year survival as thickness increases). However, the Clark cohort had a higher proportion of tumors less than 1.70 mm (141/264 [53.4%]). In the SWOG cohort, only 34.2% of tumors were less than 1.70 mm.

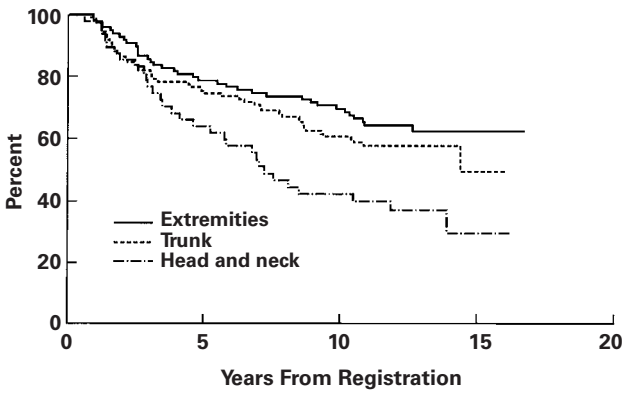

Figure 1 Overall survival by tumor site.

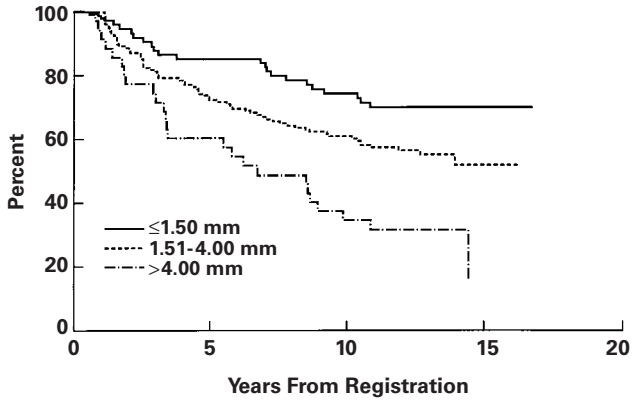

Figure 2 Overall survival by tumor thickness.

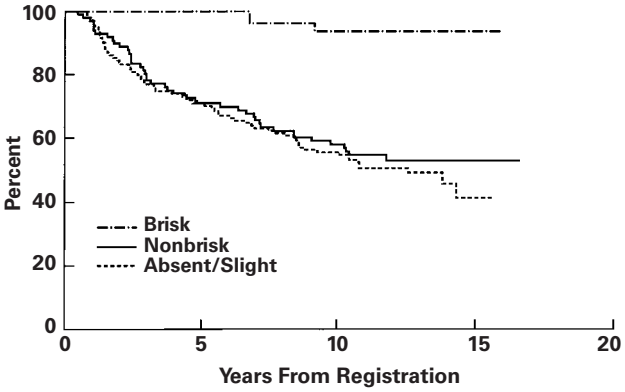

Figure 3 Overall survival by briskness of tumor-infiltrating lymphocytes.

To assess how well the Clark logistic model predicted 8-year survival in the SWOG cohort, the particular factors for each of the 240 SWOG patients were entered into the model and a predicted 8-year survival probability was computed. Results are shown in **Table 6**. Among the 166 8-year survivors, the Clark model accurately predicted survival in 121 cases (72.9%), while among the 74 patients who did not survive to 8 years, the Clark model accurately predicted early death in 32 cases (43%). The overall rate of correct predictions was 63.8% (153/240).

Discussion

There were 2 goals for this study: first, to evaluate various clinical and pathologic factors relative to patient survival, and second, to test the Clark model using a SWOG cohort of patients. For the first goal, we chose the Cox multivariate regression model in preference to the logistic regression model because it considers duration of survival. The logistic regression model considers only the binary indicator of alive or dead at a specific time point. In addition, we preselected potential prognostic factors based on previous evidence of prognostic significance, thereby reducing the likelihood of false-positive results. We found 3 factors with strong independent predictive validity: TILs, primary site, and tumor thickness.

The most significant factor was TILs (P = .005). As demonstrated in Figure 3 and Table 3, patients with a brisk host response of TILs (Image 1) had a 100% survival at 5 years and 93% survival at 10 years. In the past, other pathologists have noticed that the presence or absence of a host response in the form of a lymphocytic infiltrate may correlate with biologic outcome,[21,22] but none have attempted to grade it into categories and evaluate it statistically until Clark et al.[1] Using the same categories of TILs and analyzing patient survival with the Cox regression model, Clemente et al[23] found the presence of TILs to be an independent positive predictive factor. In the study by Clemente et al[23] of 285 patients, survival with a brisk host response of TILs was 60% at 10 years compared with a 50% survival with nonbrisk TILs and 30% survival with absent TILs. Our study

Table 3
Overall Survival by Tumor Site, Tumor Thickness, and Briskness of Tumor-Infiltrating Lymphocytes (TILs)

			Survival Estimates (%)	
	No. at Risk	No. Died	5 y	10 y
Tumor site				
Extremities	99	36	79	70
Trunk	112	47	75	61
Head and neck	48	30	64	42
Tumor thickness (mm)				
≤1.50	75	22	85	74
1.51-4.00	149	66	72	61
>4.00	35	25	60	34
Briskness of TILs				
Brisk	30	2	100	93
Nonbrisk	98	44	71	58
Absent or slight	131	67	71	55

Table 4
Overall Survival Estimates

	Survival Estimates (%)	
Factor	5 y	10 y
Age (y)		
<60	78	67
≥60	62	43
Sex		
Female	76	63
Male	73	59
Primary site		
Extremities	79	70
Trunk	75	61
Head and neck	64	42
Tumor thickness (mm)		
≤1.50	85	74
1.51-4.00	72	61
>4.00	60	34
Ulceration		
No	82	67
Yes	60	49
Lymph node dissection		
No	75	60
Yes	72	62
Histologic regression		
No	75	61
Yes	72	61
No. of mitoses		
0	100	100
1-6	77	61
≥7	66	53
Tumor-infiltrating lymphocytes		
Absent or slight	71	55
Nonbrisk	71	58
Brisk	100	93

Table 5
Actual Eight-Year Survival of the Southwest Oncology Group (SWOG) and Clark Cohorts*

Tumor Thickness (mm)	Actual 8-Year Survival Rates	
	Clark Cohort	SWOG Cohort
<1.70	87.9 (124/141)	83 (68/82)
1.70-3.60	60 (52/87)	64.9 (74/114)
>3.60	33 (12/36)	55 (24/44)
Total	71.2 (188/264)	69.2 (166/240)

* Data are given as percentage (number of survivors/total in cohort).

Table 6
Success of the Clark Model for Predicting Survival in Southwest Oncology Group Patients

Actual 8-Year Survival	Survival Prediction by the Clark Model		
	<8 y	≥8 y	Total
<8 y	32 (43%)	42	74
≥8 y	45	121 (72.9%)	166
Total	77	163	240

of 259 patients was different. Survival at 10 years was 93% with brisk TILs and 58% and 55% with nonbrisk and absent TILs, respectively. The 264 patients in the study by Clark et al[1] showed an 8-year survival of 88.5% with brisk TILs, 75.0% with nonbrisk TILs, and 59.3% with absent TILs. These differences may be accounted for by differences in patient population. In the study by Clemente et al,[23] 62% of the patients had tumors with a thickness of 3.00 mm or greater; 44% had a tumor thickness of more than 4.00 mm compared with only 13.5% in the present study. Clemente et al[23] analyzed a subset of 59 patients with a tumor thickness of less than 2.00 mm; in this subset, 10-year survival for patients with brisk TILs was 100%, for nonbrisk TILs was 77%, and for absent TILs was 45%. Recently, Busam et al[24] reported an interobserver study of TILs in melanoma; they found that the criteria can be easily taught with excellent agreement when applied to a series of cases.

Primary site was the second factor with independent predictive value ($P = .006$) and has been the subject of many multivariate analyses, but with varying results. Vollmer[10] analyzed 54 multivariate studies. The site was significant in 22, not significant in 26, and not studied in 6. A major problem for comparison is that site is coded very differently from study to study. Our study and the study by Clemente et al[23] coded site in the same way with only minor differences compared with the study by Clark et al,[1] and yet the 3 studies do not come to the same conclusions. Site was a significant independent factor in our study and the study by Clark et al,[1] but Clemente et al[23] found that, although highly significant in a univariate analysis, site was not an independent predictor of survival in a Cox multivariate analysis.

The third factor showing independent value is tumor thickness ($P = .02$). The committee preparing the proposed new AJCC staging system for cutaneous melanoma reviewed 22 studies that used the Cox model to assess prognostic factors.[9] The committee concluded that in virtually all of the studies, tumor thickness and ulceration are the strongest predictors. Vollmer,[10] in reviewing 54 multivariate studies, found that tumor thickness was the strongest predictor. In Vollmer's[10] review, ulceration was significant in 20 studies, not significant in 25, and not evaluated in 9. In our study, patients with ulceration had thicker tumors (22% with >4.00 mm) than patients with no ulceration (9% >4.00 mm; $P = .0001$ or less) and were more likely to have 7 or more mitoses (48% for ulceration vs 31% for no ulceration; $P = .002$). Similarly, increased patient age was associated with thicker tumors ($P = .008$) and primary site in the head and neck ($P = .0002$). After adjusting for these and other factors in the multivariate model, both ulceration ($P = .06$) and age ($P = .07$) were only marginally predictive of survival. Clemente et al[23] did not report on the effect of ulceration, and patient age was not predictive of survival.

Four of the factors evaluated in our study—sex, lymph node dissection, regression, and mitoses—had no independent predictive value. In the study by Clark et al,[1] sex, regression, and mitoses were independent predictors of survival. Although lymph node dissection has been found to be predictive of survival in some studies,[7,25] it did not have independent predictive value for Clark et al.[1] Vollmer's[10] review of 54 multivariate studies of melanoma included categories of sex, regression, and mitoses, but for each factor, the number of studies finding significant prognostic information was in the minority.

The clinical and pathologic data acquired for the SWOG cohort of patients in the randomized trial of vitamin A permitted us to test the Clark model. Vitamin A showed no survival benefit.[13] The vital status of each patient at 8 years of follow-up and the clinical and pathologic attributes present at the time of enrollment were entered into the model. The model correctly predicted survival in 121 (72.9%) of 166 patients and correctly predicted melanoma-specific mortality in 32 (43%) of 74 patients. The combined accuracy of prediction was 64%, less than the 83.1% accuracy found by Clark et al[1] in validating their model. The model's usefulness for predicting mortality before 8 years in our data set was especially poor.

Are there differences in patient population characteristics and methods that might account for the above? While 8-year survival was similar (71% of patients in the Clark cohort survived 8 years vs 69% of our patients) and

mortality increased with increasing thickness as in the Clark cohort (Table 5), only 34.2% of patients in our study had primary tumors less than 1.70 mm thick, whereas in the Clark cohort, 53% had primary tumors less than 1.70 mm thick. Of the other factors, our patient population included a greater proportion of male patients (56.7% vs 46%), a greater proportion of tumors with ulceration (33.3% vs 27%), fewer patients receiving prophylactic lymph node dissection (29.6% vs 45%), fewer patients with regression identified in the primary site (29.6% vs 34%), and finally, fewer patients with zero mitoses (6.7% vs 16%). Unknown synergistic effects of multiple prognostic factors also could be different between the cohorts. All of this may add up to different survival and different results when testing the Clark model. However, different patient characteristics are to be expected from any validation cohort. An effective prediction model would, necessarily, remain robust to such differences.

There are 2 potential deviations from the study by Clark et al[1] that need to be addressed. First, when the histopathologic data for the present study initially were collected, the definition of TILs by Clark et al[1] had not been published. The original pathology data included "cellular response at base." It was coded as "absent or perivascular only," "dense-patchy," and "dense-band-like." These categories corresponded exactly with the categories of TILs (absent, nonbrisk, and brisk, respectively) as defined by Clark et al.[1]

Second, mitoses were counted and coded differently. Clark et al[1] used the method of Schmoeckel and Braun-Falco.[26] More than 1.0 mm^2 of contiguous nonoverlapping fields of vertical growth was counted, until at least 1.5 mm^2 had been counted. If the vertical growth was not greater than 1.0 mm^2, the results were extrapolated to 1.0 mm^2.[1] We counted 1.0 mm^2 of vertical growth in all tumors and used adjacent step sections to achieve 1.0 mm^2 in small tumors. Also, in our study, the number of mitoses was recorded as whole numbers, whereas Clark et al[1] included decimal fractions. In the Clark model, mitoses were coded 0, 0.1 to 6.0, and greater than 6.0, and for our study they were coded 0, 1 to 6, and 7 or more. In the intermediate category, the percentage of patients was identical in the 2 studies, ie, 59%. The major difference was in the zero mitosis category: 16% for Clark et al[1] and 6.7% for our study.

It must be recognized that the present study and the study by Clark et al[1] were conducted before the widespread use of lymph node staging via sentinel lymph node biopsy. This staging procedure, incorporating serial sectioning and immunohistochemical staining of the sentinel node, is now believed by many to be the most important predictor of outcome in clinically node-negative melanoma patients.[27,28] Many of the variables used in the Clark model, but particularly tumor thickness and the presence or absence of ulceration, correlate with the likelihood of a positive sentinel lymph node. Thus, it is very possible that some prognostic factors that seem to have great independent significance in predicting outcome for clinically node-negative melanoma patients may turn out not to independently predict outcome once the sentinel node status is known. All efforts at developing prognostic models for cutaneous melanoma, including the new AJCC database,[9] ultimately will need to be reviewed and, in some cases, revised as mature outcome results for large cohorts of sentinel lymph node–staged patients become available.

Summary

We have followed up 259 patients with localized primary cutaneous melanoma for a minimum of 10 years. TILs, primary site, and tumor thickness have independent predictive value. Age and ulceration have marginal predictive value. By using the SWOG cohort of patients, we found that the Clark model has an accuracy of only 64%. Further study of the patient's immune response and TILs is warranted. We cannot recommend the routine use of the Clark model for stratifying patients as to risk of outcome. All current predictive models ultimately may need to be reexamined to include the important prognostic information obtained from sentinel lymph node biopsy procedures.

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