Lethal "Thin" Malignant Melanoma

Identifying Patients at Risk

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Thin melanomas can metastasize and be lethal. The purpose of this review was to identify negative risk factors in patients with melanomas less than 0.76 mm thick. Six hundred and eighty-one (681) such patients are reviewed in this study. Of those referred without metastatic disease (583 patients), metastases developed in 4.8% after a mean followup of 3.6 years. Of those referred with metastatic disease (98 patients), mortality was 35% after a mean followup of 5.9 years. Male patients ($p < 0.04$) and patients with axial primaries ($p < 0.05$) were at an increased risk of metastasis. Severe histologic regression was present in 40% of the primary lesions that metastasized and in only 17% of similar lesions that did not ($p < 0.001$). Increased age was associated with increased local skin metastases, but not with increased nodal or distant metastases. A prognostic model was designed, using two clinical risk factors (axial primary site and male sex) and two histologic risk factors (Clark's Level IV and severe histologic regression). The prognostic model identified a low-risk population—women with extremity primaries—with an actuarial risk of metastasis at 10 years that was less than 3%. Patients with either (1) both clinical risk factors or (2) one clinical risk factor and one histologic risk factor were identified as high-risk patients. Their actuarial risk of metastasis was 11% at 5 years and 22% at 10 years ($p = 0.0084$). Identifying high-risk and low-risk patients with thin melanomas may improve guidelines for the application of adjuvant therapies to this population.

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IN 1953, ALLEN AND SPITZ[1] made the first attempt to predict prognosis in malignant melanoma by examining a number of histologic characteristics. They noted that more superficial lesions had better prognoses. In 1969, Clark[2] designated five anatomic levels of invasion and reported, as did others,[3] that there was an increased frequency of metastasis and an increased mortality corresponding with the increasing Clark level of the primary melanoma. One year later, Breslow[4] showed that the depth of invasion of a melanoma could be easily measured with an ocular micrometer, which is more reproducible than estimating the level of invasion and contains more prognostic information than the Clark level measurement.

A number of investigators have used the dominant prognostic factor of tumor thickness to identify lesions that are less likely to metastasize and thus may be curable with simple surgical resections. In Breslow's experience, lesions less than 0.76 mm in tumor thickness (thin melanomas) did not metastasize.[5] Since that time, however, many authors[6–9] have reported metastases and mortality from thin melanomas. A recent report on the occurence of metastasis in 36 of 654 patients with thin melanomas suggests that the risk of metastasis from a thin melanoma is approximately 5%.[10]

Because significant sequelae are possible, the relatively favorable prognosis of thin melanomas, although encouraging to the patient, may be misleading. Differentiation of high- and low-risk patients with thin melanomas, therefore, has clinical importance. Because only a low percentage of thin melanoma patients experience recurrences, a large population is critical in making relevant conclusions regarding risk factors in this group. This report details our experience with 681 patients in this subgroup of melanoma patients with lesions less than 0.76 mm thick. The goals of this study were to identify clinical and histologic variables that might predict a greater likelihood of metastasic disease. Because histological regression has been a subject of debate, it was variable of special interest in our study. Another goal was to develop a comprehensive prognostic model for patients with thin melanoma that might be applica-

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ble clinically in identifying (1) the patients who truly have minimal risk of metastasis and whose disease does not warrant adjuvant therapy and (2) the patients at greatest risk of developing progressive disease, and in whom adjuvant therapy might be advised.

Patients and Methods

Characteristics of patients with thin melanomas are listed in Table 1 and are compared with those of patients with thicker melanomas (0.76 mm or greater). Since 1972, more than 5500 melanoma patients have been registered at our Cancer Center. As noted, 681 patients were identified with primary lesions less than 0.76 mm thick. This accounted for 18.5% of the 3681 patients for whom records of thickness exist. Mean followup was 4.03 years. Thirty-eight patients were followed for 10–20 years. There was a female predominance in the thin melanoma group. Black patients were rare.

Primary sites included the trunk (45.7%), extremities (39.4%), and head and neck (13.4%). Only 1.5% were on other regions, including subungual, palmar, plantar, and ocular sites. This distribution is similar to that of thicker lesions (Table 1).

Pathologic Review

A detailed pathologic review of the central cross section cut was accomplished, along with step sections from each lesion. The review included histologic type, Clark level, Breslow thickness, ulceration, the presence or absence of vascular and/or lymphatic invasion, regression, mitotic rate, pigmentation, peritumoral and intratumoral inflammation, evidence of intradermal nevus, subtumor blood vessels and host inflammatory response. Relevant findings are listed in Table 2. The slides are routinely reviewed by three pathologists, headed by one co-author (R.V.). Any discrepancies in pathologic interpretations are subjected to additional review.

Histologic regression was graded as follows and in all cases referred to only the skin adjacent to the main tumor mass. Minor inflammation (lymphocytes and macrophages) without fibrosis was graded 1; mild fibrous thickening of the papillary dermis was graded 2; and thick fibrosis with near or total absence of any melanocytes was graded 3. Grades 1, 2, and 3 are also referred to as mild, moderate, and severe regression, respectively. Each grade of regression is demonstrated in the photomicrographs of Figures 1A–C.

Treatment Received

Depending on the surgeon and anatomic site of the lesion, the primary melanomas were excised with margins of 1–5 cm. In rare cases, smaller margins were obtained. These are discussed as they relate to local recurrence. Therapeutic lymph node dissections were performed when regional nodes became clinically palpable.

If the primary lesion pathologically exhibited invasion to the junction of the papillary and reticular dermis (Level III) or deeper, the patients were treated with an adjuvant specific active immunotherapy program.[11]

TABLE 1. *Characteristics of Melanoma Patients Grouped by Thickness of the Primary Lesion*

	Thin <0.76 mm	Thicker ≥0.76 mm
Number of patients	681	3000
Proportion	18.5%	81.5%
Men:Women	0.87	1.16
Black	0.3%	1.0%
Mean age (years)	45.6	48.3
Primary site		
Trunk	45.7%	42.3%
Extremity	39.4%	36.8%
Head & Neck	13.4%	16.1%

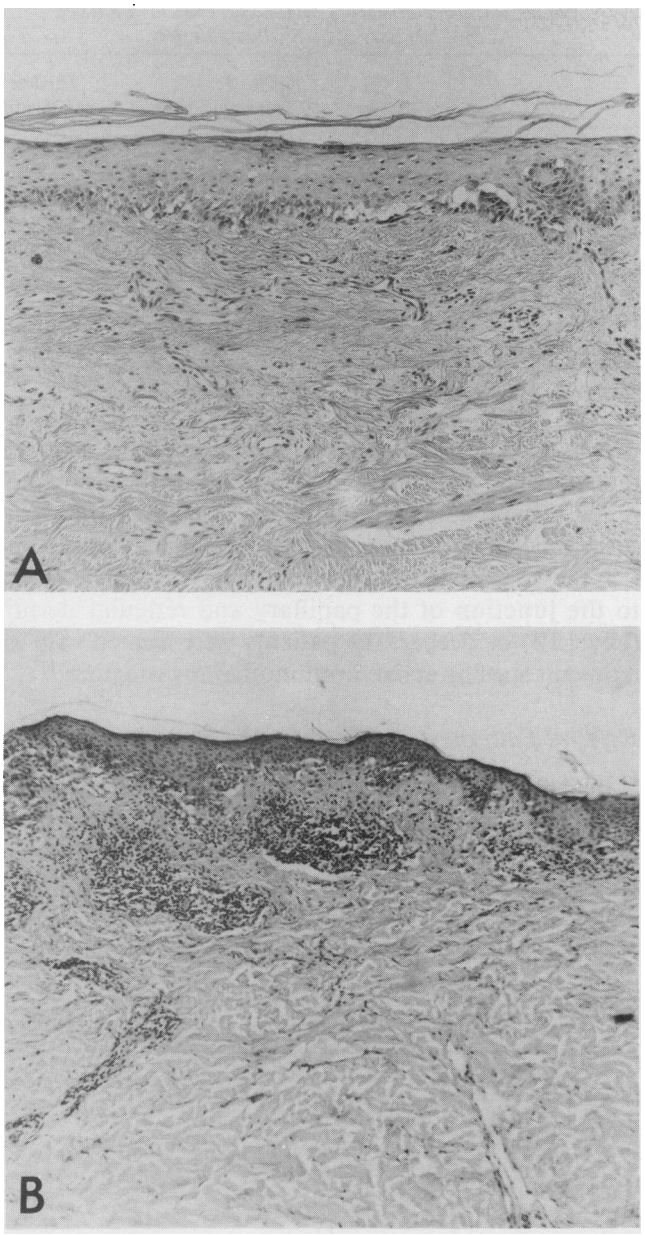
Referral Patterns and Effects on the Patient Groups

Because adjuvant immunotherapy is reserved for patients with higher risk lesions, patients with primary lesions less than 0.76 mm thick and less than Clark's Level III are not usually referred to our clinic unless they have documented metastatic disease.

Because of the selection involved in the referral of

TABLE 2. *Histologic Characteristics of Thin Melanomas*

Variable	Value	Incidence
Clark's level (n = 671)	I	1.8%
	II	35.0%
	III	56.9%
	IV	6.3%
Ulceration (n = 630)	Present	5.7%
Histologic type (n = 672)	Lentigo maligna	5.3%
	Superficial spreading	89.6%
	Nodular	1.9%
	Acral lentiginous	1.0%
Vascular invasion (n = 378)	Present	2.1%
Peritumoral inflammation (n = 380)	Absent	3.2%
Mitotic index (n = 374)	Low	89.3%
	Medium	10.2%
	High	0.5%
Regression (n = 253)	Absent	47.4%
	Mild (1)	14.6%
	Moderate (2)	18.2%
	Severe (3)	19.8%



FIGS. 1A–C. These photomicrographs represent histologic sections of thin melanomas with the various grades of regression: (A) severe regression (Grade 3), (B) moderate regression (Grade 2) at right of center, and (C) mild regression (Grade 1). All three photomicrographs are magnified 1300×.

patients with these thin lesions, several analyses evaluated patients referred with metastases separately from those referred with primary lesions only. In our series, 77% of the patients who had metastases were patients referred with metastatic disease.

Patients referred with thin primary lesions, and without evidence of local, regional, or distant metastases, were evaluated in terms of risk of metastasis. Deaths in this group were so rare during the followup period that survival is a less meaningful endpoint for discussion.

Prognostic factors known to be important for predicting metastases have also been shown to be important in predicting clinical course after metastasis.[12] Patients referred with metastatic disease were evaluated in terms of survival and the disease-free interval.

Statistical Evaluation

Actuarial disease-free interval and survival curves were constructed for the thin melanoma subgroup using the Kaplan-Meier method.[13] A Cox-Mantel rank test[14] was used to test statistical significance, with a p value of less than 0.05 considered significant. The p values reported refer to differences between survival distribu-

tions, and not simply to differences in median survival. These analyses were performed with the existing software available in the computer system of the Duke Cancer Center Data Management Unit.[15] Multivariate analyses performed on this system are Cox simultaneous proportional hazard analyses.

A Cox proportional hazard model was also used to analyze prognostic factors related to disease-free interval and survival-time in patients who did develop metastases. Selected patient groups were analysed with a chi-squared statistic and a wilcoxon rank statistic to test the prognostic significance of single variables. These analyses were performed on the Triangle Universities Computation Center computer, using the SAS system™ (SAS Institute, Cary, NC) and the programs LOGIST™ and PHGLM™ of Harrell (Clinical Biostatics, Durham, NC).

Results

Metastatic Disease

Of the total population of 681 "thin" melanoma patients, 127 (18.6%) suffered a metastasis at some point during their clinical course. This compares to 42.4% in the thicker lesions (Table 3).

Of the 583 patients referred to our center with thin primary lesions and exhibiting no evidence of metastatic disease, 28 (4.8%) had recurrences during a mean followup of 3.6 years. Ninety-eight patients had metastases before referral to our medical center. Thirty-two patients had metastases (9 local, 20 nodal, 3 distant) at the time of initial diagnosis.

The site of first metastasis was local skin in 28 patients (22.0%), regional lymph nodes in 80 (63.0%), lung in 5 (3.9%), distant skin in 4 (4.7%), gastrointestinal in 2 (1.6%), and brain, liver, and bone in one each (0.8%). This pattern of metastasis is almost identical to that of thicker lesions (Table 3).

TABLE 3. *Survival and Follow-up Data for Melanoma Patients Grouped by Thickness of the Primary Lesion*

	Thin <0.76 mm	Thicker ≥0.76 mm
Recurrence	18.6% (127)	42.4% (1273)
Site of first metastasis		
Nodes	63.0%	63.4%
Local skin	22.0%	21.1%
Lung	3.9%	5.5%
Other	11.0%	10.0%
Mortality	8.7% (59)	22.5% (675)

Local Recurrence

Local skin metastasis is defined as the presence of a metastatic tumor deposit within 5 cm of the primary tumor or its scar. Local recurrences are a subset of local skin metastases and refer to recurrences that appear after excision of the primary melanoma and which are in skin or subcutaneous tissue within 5 cm of the scar.

Thirty-five patients (5.1% of the patients with thin melanomas) developed local skin metastases from thin melanomas. Ten had satellite lesions at the time of initial diagnosis, and the remaining 25 patients (3.7%) had local recurrences. Thirteen of these 25 had recurrences within the scar, and the remainder recurred within 5 cm of the scar.

The time from excision of the primary lesion to that excision of the local recurrence was less than 6 months for four patients; between 6 months and 2 years for eight patients; between 2 and 5 years for five patients, and more than 5 years for eight patients. One local recurrence occurred 14.7 years after excision of the primary lesion.

Four of the lesions that recurred were initially misdiagnosed as benign; therefore, wide excisions were not performed. The retrospective review of the original slides revealed the correct diagnosis of the initial lesion to be melanoma. In these four cases, the mean time from excision of the primary lesion to excision of the local recurrence was 4.7 years.

There were 21 cases in which there were local recurrences after correct initial diagnosis. Margins of excision were determined as the least diameter of the wide excision specimen, or the smallest measured margin, as reported by the pathologist. Of the lesions that developed local recurrence, those with margins less than 1 cm recurred no sooner than those with wider margins: ten cases with margins less than 1 cm recurred after a mean of 3.4 years; nine cases with margins of 1 cm or greater recurred after a mean of 2.4 years.

Survival

Actuarial five-year survival was 92%. There were 59 deaths in the series. The causal relationship between the melanoma and mortality is known for 47 patients. Of these, 40 deaths (85%) are attributed either to the melanoma itself or to treatments for the melanoma. Seven deaths are attributed to unrelated causes.

Prognostic Factors Relevant to the Clinical Course

With thin melanomas, the prognostic difference between axial and extremity lesions was marked. Five- and 10-year actuarial survivals were 94 and 87%, respec-

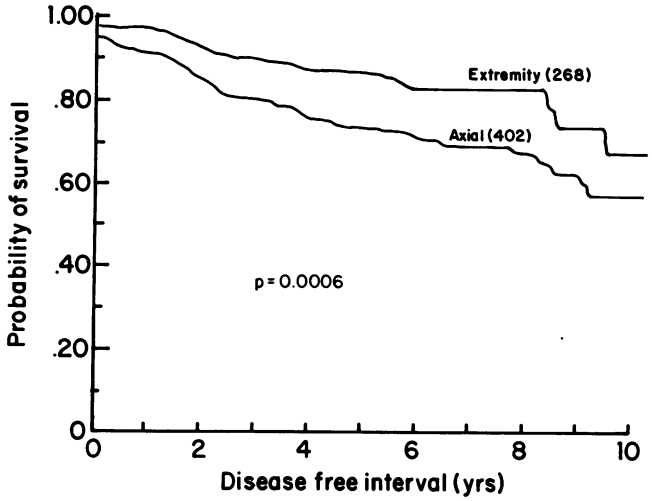


FIG. 2. Thin melanomas arising in axial sites are associated with a shorter disease-free interval (DFI) than those arising in extremity sites (p = 0.0006).

tively, for patients with extremity lesions, and 91 and 63%, respectively, for those with axial lesions. Disease-free interval (DFI) was also significantly shorter for patients with axial primaries (Fig. 2). The prognostic significance is outlined in Table 4.

Male patients had shorter disease-free interval than females (p = 0.02, Fig. 3).

Overall DFI tended to be shorter for patients who, at the time of diagnosis, were more than 50 years old than for those 50 years old or younger (p = 0.065). Within the group of patients in whom metastases had developed before referral to our medical center, patients had a shorter DFI (median 0.8 years) if they were more than 50 years old than if their age was 50 or less (median DFI = 2.2 years).

An increased risk of local skin metastasis accounts for the increased metastatic risk in older patients with thin melanomas. There is no significant age-related difference in distant DFI or nodal DFI. (Table 5). This is evidenced further in Figure 4; with advancing age, the prevalence of local skin metastases—which occurred at any time during the patient's course—was markedly increased, whereas the prevalence of nodal metastases was slightly decreased. There was no difference in the prevalence of distant metastases.

The histologic type of thin melanomas was superficial spreading in 90% of the patients, lentigo maligna in 5%, nodular in 2%, and acral lentiginous in 1%. The nodular melanomas were associated with a greater frequency of metastasis and mortality, but the number of patients with this entity were too few to demonstrate any statistical significance.

Thickness of the melanomas, within the 0 to 0.76 mm range, appear to have no consistent association with metastatic disease. Lesions 0.25 to 0.40 mm thick had a shorter DFI than patients with thinner (<0.25 mm) or thicker (>0.40 mm) lesions. Also, DFI was shorter for Level II lesions than for Level III lesions (p < 0.0001). As discussed above, these results are attributed to patterns of referral and follow-up, which uniquely affect the variables of thickness and Clark's Level (II *vs.* III).

The presence of severe (Grade III) regression was associated with a significant shortening of DFI (p = 0.0013). The actuarial DFI curves for thin melanomas with severe regression could not be distinguished from those of thicker (>0.76 mm) lesions (p > 0.54, Fig. 5).

The absence of peritumoral inflammation was associated with a shorter DFI (p = 0.0322) and poorer survival (p = 0.0001), but was found in twelve patients only (Table 4).

TABLE 4. *Univariate Analysis of Prognostic Criteria in Patients with Thin Melanomas*

	Prognostic Significance*			
	DFI		Survival after Diagnosis	
Negative Prognostic Criteria	All Patients	Referred without Metastasis	All Patients	Referred with Metastasis
Male Sex	0.0202	0.0381	0.1223	NS
Clarks Level IV	NS	NS	0.0336	0.0383
Axial *vs.* extremity	0.0006	0.0452	0.0042	0.0188
Ulcer present	NS	NS	NS	NS
No peritum. infl	0.0322	NS	0.0001	0.0037
Increased mitoses	0.1518	—	NS	NS
Severe regression	0.0013	0.1023	NS	NS
Multiple primaries	0.0407	NS	NS	NS
Age > 50 years	0.0647	0.0650	—	—

* All p values are derived from Cox-Mantel rank testing of actuarial survival and DFI curves. NS: p > 0.25.

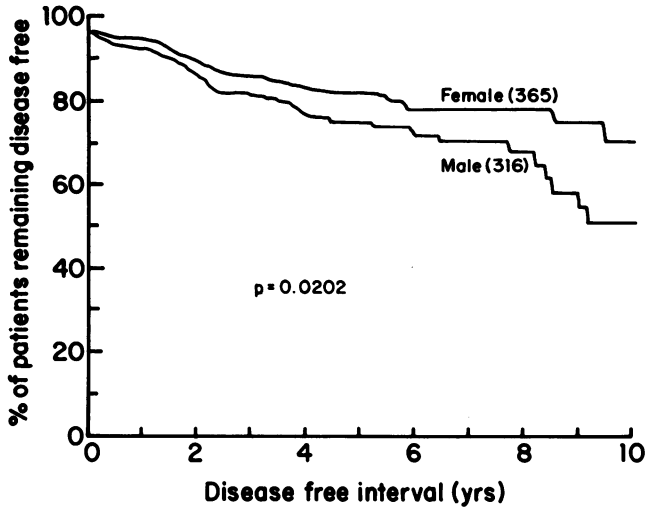


FIG. 3. Male patients have a shorter DFI than female patients (p = 0.0202).

Multiple primary melanomas were found in 36 patients, and there was a association with metastasis, but not with survival (Table 4). The patients were managed and reviewed on the basis of the thickest lesion present.

Comparisons of Metastasizing and Nonmetastasizing Lesions

Characteristics of tumors that metastasized were compared to those of tumors that did not metastasize. This analysis included only Caucasian, nonpregnant patients whose primary sites included head, neck, trunk, or extremities (excluding acral). Of the tumors that did not metastasize, only those with the longest follow-up were considered. This resulted in similar median follow-up times for the two groups. Histologic regression was graded in over half of these patients.

Tumors that metastasized are compared with those that did not (Table 6). Metastatic lesions were more often axial, occurred more often in males, and more often showed severe regression than lesions that did not metastasize.

The metastasizing tumors were also significantly thinner and of a lower level than those that did not metastasize. This appears to be an artifact, resulting from the patterns of patient selection and follow-up, as discussed above.

Patients Referred Without Metastatic Disease

Patients referred on the basis of their primary lesion alone were believed to represent best the typical experience with thin melanomas. There were 583 patients in this group. Their actuarial 5-year survival was 96%. Within this group, 41% had extremity primaries and 57% had axial primaries. Actuarial DFI was shorter for patients with axial lesions ($p = 0.045$) and male patients ($p < 0.04$). Clinical and histologic characteristics of these patients are detailed in Table 7.

TABLE 5. *Prognostic Differences Relating Age to Metastasis: Comparing Patients More Than 50 Years Old to Patients 50 Years Old or Younger*

p values (Cox-Mantel)	Referred with Metastasis	Referred without Metastasis
Local DFI	0.0005	0.0473
Nodal DFI	0.5065	0.2230
Distant DFI	0.4772	0.2526
Overall DFI	0.0064	0.0650

Breslow thickness ($p > 0.29$), peritumoral inflammation ($p > 0.41$), ulceration of the primary lesion ($p > 0.88$), and the presence of multiple primary lesions ($p > 0.25$) had no significant impact on the risk of metastasis in this subgroup of 583 patients. There were too few patients with vascular invasion for assessing its significance.

Clark's level did have prognostic significance with regard to metastasis, but Level II lesions had a shorter DFI than Level III lesions ($p = 0.021$). The number of Level IV lesions was relatively small (35), and no significant difference could be demonstrated for Level IV lesions when compared with Level III ($p > 0.60$) or Level II ($p > 0.40$) lesions.

In 214 patients, regression was graded. Those with severe regression ($n = 35$) had a 72% disease-free survival at 5 years. Patients in whom regression was absent,

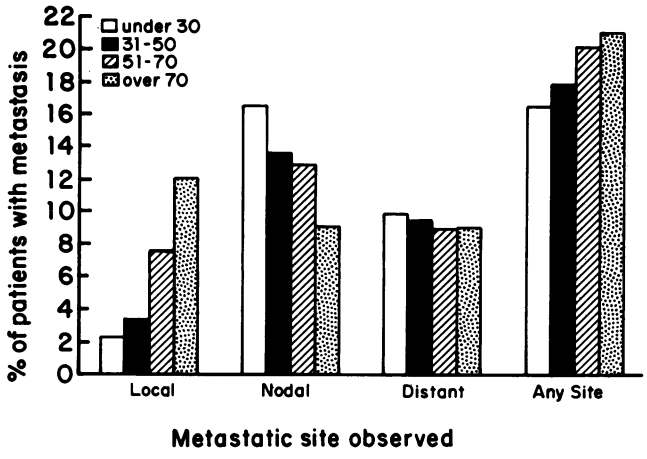


FIG. 4. The percentage of patients with local, nodal, or distant metastases that occurred at any time during the follow-up period are presented for each age group of patients with thin melanomas. The total percentage of patients with any form of metastatic disease is also presented for each age group. The only significant differences are for the occurrence of local metastases (chi-square = 8.33, 3df, $p = 0.039$), which increases with advanced age.

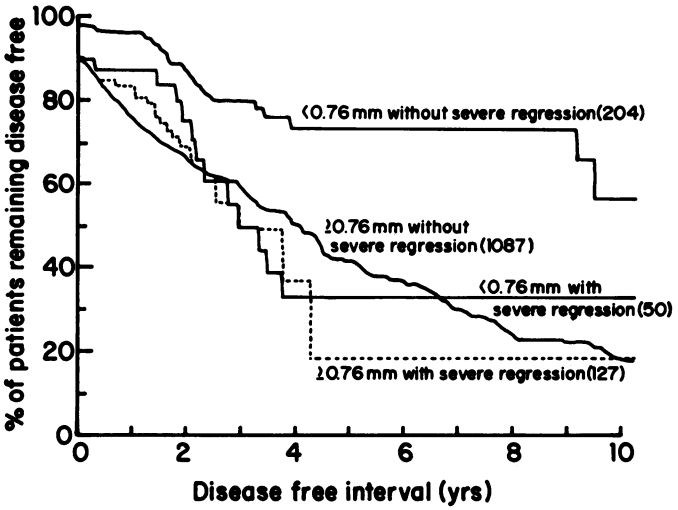


FIG. 5. Actuarial DFI is plotted for thin melanomas (less than 0.76 mm) with and without severe regression, and for thick melanomas (0.76 mm or greater) with and without severe regression. The prognosis of thin melanoma patients with severe regression resembles that of patients with thicker lesions. Thin lesions without severe regression have a better prognosis than thin lesions with severe regression ($p = 0.0013$).

mild, or moderate had a 94% disease-free survival at 5 years (actuarial). The difference approached significance ($p = 0.1023$, Table 4). The presence of ungraded regression had no impact on disease-free survival.

Patients Referred with Metastatic Disease

Of the patients referred with metastatic disease (96), 34 (35%) died during the follow-up period. There was a predominance of axial lesions (70%), which were associated with shorter survival from the date of initial diagnosis ($p = 0.0188$, Table 4), as compared to extremity lesions.

Clark's Level IV lesions had a poorer prognosis than Level III lesions ($p = 0.0383$), with median survivals of 4.4 and 10.5 years, respectively (Fig. 6). Survival for patients with Clark's Level II and Clark's Level III lesions did not differ ($p > 0.92$).

Breslow thickness did not have a relationship with survival within this group ($p > 0.25$). Other evaluations within this subgroup are detailed in Table 4.

Mortality, after a mean follow-up of more than 5 years after diagnosis, was 33%. Forty-five patients (47%) developed further metastatic disease after their initial metastases that led to referral to our clinic. The clinical and histologic characteristics of these patients are listed in Table 7, segregated on the basis of the site of the primary melanoma.

Site of Metastasis and Association with Prognostic Variables

The frequency of developing local, nodal, and metastatic disease during the course of follow-up revealed several interesting findings. As has been discussed, males were more likely to develop metastases from thin melanomas than females. The increased incidence of metastasis for males ($p < 0.05$, chi-squared) appears to be a reflection primarily of an increased frequency of nodal metastases ($p < 0.01$, Table 8).

As noted earlier, local metastases were prone to develop in elderly patients in greater frequency than in younger patients, without an increase in other metastatic sites.

The increase in metastases from axial primaries appeared to be distributed among local, nodal, and distant sites. The same was observed with severe regression (Table 8).

Prognostic Model

A prognostic model was designed to identify patients at high, intermediate, or low risk of metastatic disease from a primary lesion less than 0.76 mm thick. A multivariate analysis produced a risk equation, but this was no more useful in establishing a prognostic model than a more empiric approach. Increased age was associated with greater risk of metastasis, but in the absence of an age-related difference in distant and nodal metastasis, there was a disproportionate incidence of local metastasis. A skewing of risk prediction toward the risk of local metastasis was not considered as relevant to the prediction of long-term prognosis; therefore, age was not included in the prognostic model. Two clinical variables were included (sex of the patient, and site of the primary lesion). Two histologic variables were also included (the presence of severe regression, and a Clark's Level of IV). The selection of the two clinical variables was based on their significant association with metastasis (Table 4).

TABLE 6. *Retrospective Analysis of Metastatic and Nonmetastatic Lesions*

Factor	Metastatic	Nonmetastatic	Chi-square p value
N	104	360	
Mean F/U (days)	2001	1724	
Median F/U (days)	1636	1656	
Axial	72%	54%	0.001
Men	55%	43%	0.03
Ave Thickness	0.52 mm	0.57 mm	0.0007 (wilcoxon)
Level > II	57%	81%	0.001
Severe Regression	40%	17%	0.004
Ulcerated	8%	7%	NS

NS: $p > 0.05$.

TABLE 7. *Clinical and Histologic Characteristics*

	Referred with Metastasis		Referred without Metastasis	
Primary site:	Extremity	Axial	Extremity	Axial
Number of patients	27	69	241	333
Men:Women	0.59	1.5	0.37	1.4
Black	0.0%	0.0%	0.8%	0.0%
Mean age (years)	45.0	45.8	46.5	44.5
Primary site				
Upper extremity	44%		46%	
Lower extremity	56%		54%	
Trunk		75%		78%
Head and neck		25%		22%
Metastasized	100%	100%	2.9%	6.3%
Site of first metastasis				
Local	37%	18%	29%	14%
Nodes	56%	70%	43%	55%
Distant	7%	11%	29%	32%
Mortality	26%	38%	3%	5%
Mean follow-up	8.2 yr	5.0 yr	3.7 yr	3.5 yr
Progressing	30%	54%	2.9%	6.3%
Ulceration	0%	6%	6%	5%
Clark's Level				
I	0%	3%	3%	1%
II	22%	51%	27%	38%
III	59%	41%	62%	55%
IV	11%	4%	7%	5%
Severe regression	0%	47%	13%	19%
Vascular invasion	17%	8%	1%	1%

Although the effect of sex was not statistically significant in the multivariate analysis, inclusion of both sex and site produced a more reliable model. The selection of severe regression was based on its significant effect on DFI (Table 4) and its prevalence in lesions that metastasized (Table 6), especially axial lesions, while being rare in nonmetastatic lesions. A Clark's Level of IV was associated with greater mortality from thin melanomas (Table 4).

Three risk groups were defined as follows:

Low-risk: All female patients with extremity primaries (no clinical risk factors).

Intermediate-risk: All patients with one clinical risk factor (male *or* axial) and without either histologic risk factor (severe regression not present, and Clark's Level less than IV).

High-risk:
a) Patients with both clinical risk factors (men *and* axial).
b) All patients with one clinical risk factor *and* one or more histologic risk factors (Level IV, severe regression).

Patients may also be assigned to risk groups by assigning point values for each variable, as follows: men (2), axial (2), severe regression or greater than level IV (1). Low-risk is 0–1 point. Intermediate-risk is 2 points. High-risk is 3 or more points. Patients with acral and mucocutaneous primaries are believed to be at greater risk than those extremity primaries, but are too uncommon at this thickness to be adequately addressed. They are grouped with axial primaries for the purposes of the model.

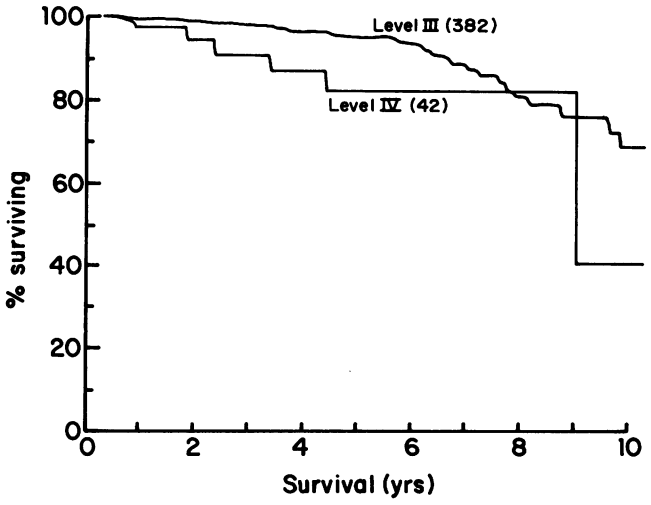


FIG. 6. Patients with thin Clark's Level IV melanomas have a poorer survival rate than patients with thin Clark's Level III lesions ($p = 0.0336$).

TABLE 8. *Frequency of Outcomes of Disease in Subsets of Patients with Thin Melanomas During Mean Follow-up of 4 Years*

	Frequency of Metastasis (%)				
	Overall	Local	Nodes	Distant	Mortality
Overall	18.6	5.1	13.5	9.4	8.7
Sex					
Male	21.8*	4.4	17.4†	9.2	10.1
Female	15.9	5.8	10.1	9.6	7.4
Pregnant	31.2	0.0	31.2	13.3	6.3
Age (years)					
0–30	16.5	2.2	16.5	9.9	11.0
31–50	17.9	3.4	13.6	9.6	7.7
51–70	20.2	7.7	12.9	9.0	7.7
>70	21.2	12.1*	9.1	9.1	18.2
Primary site					
Axial	22.4†	5.3	16.7†	11.9†	10.2*
Extremity	12.7	4.9	8.6	5.6	5.6
Thickness (mm)					
0.0–0.25	11.5	7.7	3.8	0.0	0.0
0.25–0.4	20.2	1.0	15.4	11.5	6.7
0.4–0.6	20.7	6.0	14.7	11.7	9.8
0.6–0.76	16.8	5.6	12.6	7.4	9.1
Vascular invasion					
Absent	16.5	3.5	12.4	8.9	7.6
Present (n = 8)	62.5†	25.0*	62.5†	37.5*	37.5*
Ulcer	19.4	8.3	19.4	13.9	13.9
Histology					
LMM	19.4	11.1	11.1	5.6	8.3
SSM	17.4	4.4	12.8	8.7	9.5
NM	46.2	23.1	30.8	23.1	15.4
ALM (n = 7)	28.6	0.0	14.3	28.6	14.3
Clark's Level					
I	16.7	0.0	16.7	16.7	8.3
II	22.6	5.1	16.6	11.1	7.2
III	15.4	5.2	11.0	7.3	8.6
IV	21.4	7.1	14.3	14.3	16.7
Mitotic rate					
Low	18.3	3.3	14.1	9.9	7.2
Medium	15.8	5.3	15.8	10.5	15.8
Absence of peritumoral inflammation	33.3	0.0	33.3	16.7	25.0
Severe Regression					
Absent	14.8	3.0	10.8	7.9	5.9
Present	36.0‡	6.0	28.0†	18.0*	10.0
Mult primary	30.6	5.6	19.4	16.7	8.3

Asterisks mark variables with greater risk:
* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.

Application of the model to patients referred without metastatic disease resulted in three different actuarial curves for DFI (Fig. 7). Actuarial risk of metastasis is 2.9% at 5 years for the low-risk group, and rises to 6.2 and 11% for the intermediate- and high-risk groups, respectively. At 10 years, those risks are 2.9, 6.2, and 22%. The high- and low-risk curves are significantly different ($p = 0.0084$).

The actual observed rate of metastasis among the low-, intermediate-, and high-risk groups were 2.3, 3.8, and 8.0% (chi-squared 7.54, $p < 0.023$) during a mean follow-up of approximately 3.5 years for each group.

Within the group of patients referred with metastatic disease, DFI was less for low-risk patients than for intermediate- and high-risk patients ($p = 0.035$, $p = 0.0561$, respectively, Fig. 8).

Application of the model to the entire population also successfully segregates the population into three risk groups (Fig. 9). The actuarial risks of metastasis at 5 years were 10, 22, and 30%, for low-, intermediate-, and high-risk groups. The low-risk and high-risk curves were significantly different ($p < 0.0001$).

Discussion

Thin melanomas (less than 0.76 mm) do have a markedly better prognosis than thick lesions, but in recent years there has been a reassessment of the early reports

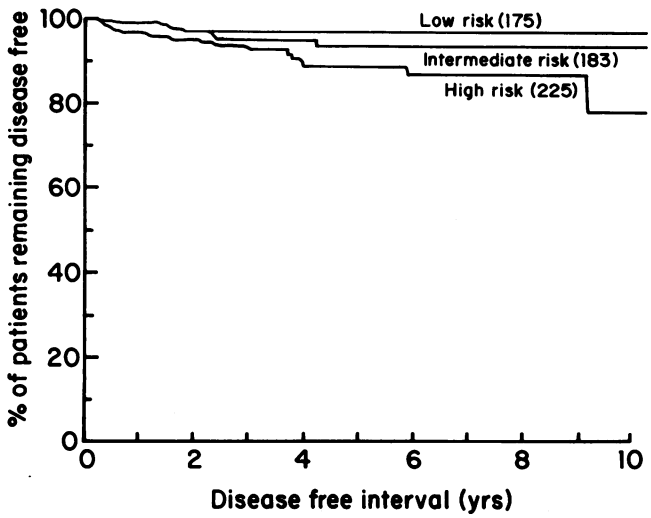


FIG. 7. The prognostic model is applied to patients with thin melanomas who were referred without metastatic disease (n = 583). Actuarial DFIs are plotted for high-intermediate-, and low-risk patients. The model successfully differentiates high- and low-risk patients in terms of their observed risk of metastasis (p = 0.0084).

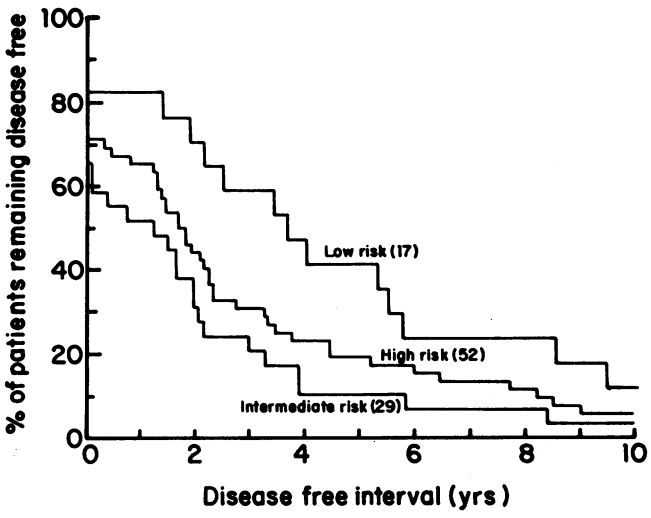


FIG. 8. The prognostic model is applied to patients with thin melanomas who were referred with metastatic disease (n = 98). Actuarial DFIs are plotted for high-intermediate-, and low-risk patients. The low-risk patients have prolonged disease-free survival compared to the intermediate-risk (p = 0.035) and the high-risk (p = 0.056) patients. High- and intermediate-risk patients cannot be differentiated in terms of time to metastasis.

that these thin lesions never recur after simple excision.[16] In our series, 18.6% of the patients with the "thin" melanomas experienced metastatic disease, despite adequate excision of the thin primaries.

Breslow suggested that the lethal "thin" melanomas may have been inadequately studied, and he recommended a 1–2 mm interval between step tissue sections. Concerning sampling error, Sondergaard[17] has reported 95% consistency in histologic type, Clark Level, and tumor thickness when the central cross-section of the tumors was taken as representative of the lesion, when compared with step-sectioning at 1–2 mm intervals. Furthermore, Woods has reported 12 metastatic melanomas that measured less than 0.76 mm on multiple sections, 11 of which resulted in death.[18] The experience of the Sydney Melanoma Unit included 61 recurrences and 41 deaths in 846 patients with Stage I melanomas less than 0.76 mm thick.[19] It is our belief that a subset of the thin melanomas are, indeed, lethal.

Local recurrences occurred in 25 cases, but there was no evidence that wide margins greater than 1 cm were any more likely to effect local control than narrow margins of a centimeter or less. Several thin melanomas recurred locally despite wide margins, and the time to local recurrence did not depend on the margin of excision. Furthermore, the vast majority of first metastases (78%) were to nodal or distant sites, suggesting that factors other than the adequacy of local control are the principal determinants of risk from a thin melanoma. At present, it appears that margins of 1–2 cm, which in most cases permit primary closure, are adequate for surgical management of thin melanomas.

Both the sex of the patient and the site of the primary lesion were found to be significant variables in the metastasis of thin melanomas. A limited multivariate analysis failed to show independence of these variables, but the presence of both risk factors was associated with greater risk than the presence of either one of these risk factors alone. Similarly, previous work has demonstrated that site, as well as patient sex, has had prognos-

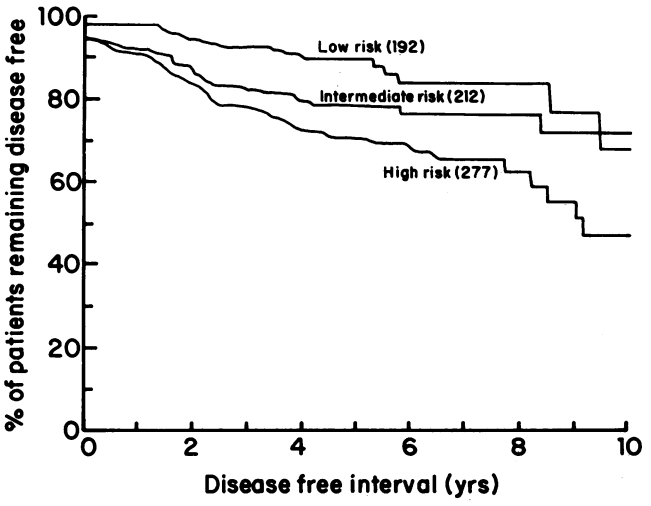


FIG. 9. The prognostic model is applied to the entire population of patients with thin melanomas (n = 681). Actuarial DFIs are plotted for the patient subsets identified in the model as high-, intermediate-, and low-risk patients. The DFIs of high-risk patients are significantly shorter than those of patients at intermediate risk (p = 0.0245) or low risk (p < 0.0001).

tic significance.[20] The negative prognostic value of an axial primary has been identified by the Sydney group, as well, and although they report a higher frequency of recurrence in men than in women, they do not address the significance of that difference.[19]

Mitotic index has been associated with prognosis in previous reports,[19,20] but no effect could be demonstrated in the present review. That may be explained partly by our method of recording mitotic index in a qualitative, rather than a quantitative, manner. Certainly, it is biologically consistent that a lesion with high mitotic activity may be associated with an aggressive clinical course.

Older patients were more likely to develop metastatic lesions than younger patients, but a significant increase in local metastases explained the differences. Nodal and distant metastases were no more prevalent in older patients than in younger patients.

A common finding in the primary tumors is that many showed signs of severe regression, which implies that at one time that they were thicker lesions. Previous reports have been conflicting. Some have found no significant association between regression and recurrence[19,21] nor between regression and survival.[25] Others have noted an association of regression with recurrent thin lesions.[7,10,23]

Grading of regression, however, reveals a subset of patients: those with severe regression, who have a much higher risk of recurrence. Presumably, the regressed lesion was thicker some time before its excision and had the metastatic potential of a thicker lesion. This is supported by the finding that patients with regressed thin lesions have a prognosis equivalent to that of a nonregressed thicker lesion (Fig. 5).

The differences in previous reports regarding the role of regression in evaluating thin melanomas for risk of metastasis may be related to differences in definitions of regression. Our grading system does identify a subset at risk. This is in accordance with previous work,[24] which found, in lesions less than 1 mm thick, that 10-year survival was adversely affected by regression with fibrotic scar, but not by active regression without fibrotic scar. That work found that the thicker and wider the scar, the poorer the survival.

Because of its association with greater mortality among patients referred with metastatic disease, a Clark's Level of IV is considered a risk factor. Other investigators have also found that Level IV lesions have a poorer prognosis, when considering lesions ranging in thickness from 0.6 to 1.1 mm.[25]

Our finding that, in terms of metastasis, Level II lesions had a poorer prognosis than Level III lesions is in conflict with the experience of others.[19] It is likely that the finding represents artifact relating to treatment and referral patterns, which uniquely affect the differentiation between Level II and Level III lesions. A reasonable explanation relates to the fact that most of the patients with Level III thin melanomas were treated with adjuvant specific active immunotherapy (ASAI), whereas the large majority of those with Level II lesions were not. A possible therapeutic advantage of specific active immunotherapy as an adjuvant therapy in this setting is suggested.

Male patients and patients with axial primary melanomas are at significantly greater risk of recurrence than women with extremity primaries. The relative patient risk may be determined by the proposed model. Women with extremity primaries less than 0.76 mm thick (low-risk) may expect a 2–3% risk of recurrence over the ensuing 5 years. Males with axial primaries, and others in the high-risk group because of histologic factors, may expect a 10–20% risk of metastasis at 5 years.

These groups must be considered separately when formulating plans for surgical treatment and adjuvant therapies. A woman with an extremity primary can be reassured by her favorable prognosis. On the other hand, the presence of severe regression or a Clark's Level of IV in a thin melanoma arising in a man or on an axial site may indicate that a more aggressive therapy is needed than has traditionally been used in the management of thin melanomas. The same recommendation applies to any axial thin melanoma in a male patient. The appropriate adjuvant therapy may include elective lymph node dissection, as suggested by others,[19] or may include adjuvant specific active immunotherapy.

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