Prognostic Factors for Melanoma Patients with Lesions 0.76–1.69 mm in Thickness

An Appraisal of "Thin" Level IV Lesions*

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Fourteen variables were tested for their prognostic usefulness in 203 patients with clinical Stage I melanoma and primary tumors 0.76–1.69 mm thick. Only two variables, primary tumor location and level of invasion, were useful in predicting death from melanoma for these patients. Of the 12 deaths from melanoma, 11 occurred in patients with primary tumors located on the upper *b*ack, posterior *a*rm, posterior *n*eck, and posterior *s*calp (=BANS). There has been only one death from melanoma in 136 patients with melanoma located at other sites (11/67 vs 1/136, $p < 0.0001$ Fisher's Exact Test). Of the 67 BANS patients, 51 had level II or level III lesions and five (10%) died of melanoma. This compares with six deaths from melanoma in 16 patients (37.5%) with level IV BANS lesions (5/51 vs 6/16, $p = 0.01$ Fisher's Exact Test). The relatively high incidence of both melanoma deaths and regional node metastases for the BANS group merits consideration for testing the efficacy of elective regional node dissection for these patients.

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A PATIENT WITH CLINICAL STAGE I melanoma 0.76–1.5mm in thickness has a 90% chance of cure by wide local excision (WLE) of the primary tumor.[5,13,15] For most physicians, this high survival rate eliminates this patient from consideration of additional treatment such as elective regional node dissection (ERND) or adjuvant therapy. From the patient's point of view, however, WLE alone may seem inadequate in the context of a one in ten chance for melanoma death. The identification of high risk and low risk subpopulations within this thickness range, then, is a prerequisite for more appropriate tailoring of treatment to outcome.

With this goal in mind, 14 prognostic factors were examined in 203 patients with clinical Stage I melanoma 0.76–1.69 mm in thickness. A thickness of 1.69 mm rather than 1.50 mm was chosen because the natural thickness breakpoints for clinical Stage I patients with lesions >0.75 mm occur at ≥1.70 mm and ≥3.65 mm.[19]

Patients and Methods

Between September 1, 1972 and May 30, 1977, 644 patients with primary cutaneous malignant melanoma were consecutively evaluated and prospectively entered into a natural history study at either New York University Medical Center or the Massachusetts General

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Hospital. More detailed characteristics of this study are described elsewhere.[9-14,23] Histologic sections were reviewed by one pathologist.

Of the 644 patients entered into the study, 203 had clinical Stage I melanoma 0.76–1.69 mm in thickness, and these 203 patients are the subject of this paper. Fourteen variables were tested for their usefulness in predicting death from melanoma (Table 1). These variables are described in detail in previous studies.[9-12,14,23] Kaplan-Meier life tables.[17] as well as a Cox (multivariate) proportional hazards analysis[2-4,7-12,14] were done. However, only 12 of the 203 patients in this series died of melanoma. Therefore, for clarity, the data were presented as 2 × 2 contingency tables with probability-values determined by the Fisher's Exact Test.[16] This left the significance of factors and combinations of factors unchanged. The mean follow-up time for patients who did not die of melanoma were comparable within the examined subcategories.

TABLE 1. *Variables Tested for Prognostic Value In 203 Patients With Clinical Stage I Melanoma 0.75–1.69 mm in Thickness*

Clinical variables
sex
age
location
adjuvant therapy received
surgical treatment
[wide local excision (WLE) vs elective regional node dissection (ERND)]
Histologic variables tested
level of invasion[6]
thickness[5]
histologic type[6,22]
histologic ulceration[2-4]
mitoses/mm^2 [2-14,23]
microscopic satellites[13]
lymphocyte response
histologic regression[17]
pathologic stage

Results

Of 203 patients evaluated (Tables 2 and 3), 11 died of melanoma and one patient is alive with a brain metastasis.* One additional patient is alive and free of disease after surgical removal of a distant skin metastasis, and another patient is free of disease after surgical removal of a recurrence in the regional lymph nodes. None of the remaining 189 patients had recurrent disease following initial primary treatment. Of these 189 patients, 97% had at least three years of follow-up, 85% were followed four or more years, and 55% had at least five years of follow-up.

Examination of the body charts revealed that 11 of the 12 patients who died of melanoma each had their primary tumor located in the following contiguous area: upper *b*ack, posterior *a*rm, posterior *n*eck, and posterior *s*calp (BANS). Of the 67 patients in this group, 11 (16%) died of melanoma. This compares with only one death in the remaining 136 patients (11/67 vs 1/136, <0.0001 Fisher's Exact Test). There were significantly more superficical spreading melanomas ($p = 0.05$ chi-square) and significantly more males ($p = 0.05$, chi-square) in the BANS group than the nonBANS patients. Other than histologic type and sex, there were no significant differences in either the primary tumor pathologic factors or the clinical characteristics between the patients with lesions in the BANS group and patients with lesions at other sites to account for differences in survival (Table 3).

That there were more microscopic lymph node metastases found at the time of elective regional node dissection for BANS patients is further evidence of the tendency for thin BANS lesions to metastasize. Of the 40 patients in the BANS group who had ERND, four had microscopic deposits of tumor in the removed lymph nodes, and one patient, with a lesion near the midline, subsequently developed a metastasis to the contralateral lymph node group. Of the remaining 27 BANS patients treated with WLE only, three subsequently developed nodal metastases. Thus, eight of the 67 patients (12%) in the BANS group had nodal metastases. For patients with lesions at other sites, only one of 84 (1.2%) had microscopic metastases in regional lymph nodes at the time of ERND. None of the 50 patients with non-BANS lesions treated with WLE only subsequently developed nodal metastases (8/67 vs 1/136, $p < 0.01$, Fisher's Exact Text).

The only other prognostically useful variable for the entire group of 203 patients in this study was level of invasion. Of the 60 patients with level IV lesions, seven (12%) died of melanoma. This compares with five melanoma deaths in the remaining 143 patients {7/60 vs 5/143, $p = 0.01$ Fisher's Exact Text}. Level of invasion was particularly useful for the BANS patients. Of the 16 patients in this group with level IV lesions 6 (37.5%) died of melanoma. This compares with five deaths in 51 patients (10%) with level II or level III BANS lesions (6/16 vs 5/51, $p < 0.05$ Fisher's Exact Test).

Thus, the prognostic model for the entire 203 patients in this series was comprised of only two variables: specific location and level of invasion (Table 4).

Discussion

One explanation for the location findings is simply that BANS lesions might tend to be ignored longer than lesions at other sites. The question then is why do such lesions not get thicker (as do other melanomas) as they develop the propensity to metastasize? Either a subset

* We have assumed that the patient with brain metastases will eventually die of melanoma (*i.e.* that patient is one of the 11 listed as "dead" to simplify wording).

TABLE 2. *Single Variable Results For 203 Patients With Clinical Stage I Melanoma 0.76–1.69 mm in Thickness*

Variable	Number of Patients in This Category	Number Dead of Melanoma and Per Cent in Total	p-Value†
Histologic type			
lentigo maligna melanoma	8	0 (0%)	NS
nodular melanoma	19	2 (10.5%)	
acral lentiginous melanoma	8	0 (0%)	
superficial spreading melanoma	159	9 (6%)	
indeterminate	9	1 (11%)	
Level of invasion			
level II	24	1 (4%)	<0.05
level III	119	4 (3%)	(LIV vs LII & LIII)
level IV	60	7 (12%)	
level V	0	—	
Histologic ulceration			
yes	42	3 (7%)	NS
no	161	9 (6%)	
Mitoses/mm^2			
0–6	195	12 (6%)	NS
>6	8	0 (0%)	
Lymphocyte response			
nearly absent, minimal, or moderate	148	10 (7%)	NS
marked	55	2 (4%)	
Location			
BANS locations*	67	11 (16%)	<0.0001
Non-BANS locations	136	1 (<1%)	
Histologic regression			
absent	96	3 (3%)	NS
present	107	9 (8%)	
Primary tumor thickness			
0.76–1.25 mm	141	9 (6%)	NS
1.26–1.65 mm	62	3 (5%)	
Microscopic satellites			
absent	193	11 (6%)	NS
present	10	1 (10%)	
Pathologic stage			
positive nodes	5	1 (20%)	NS
negative nodes	119	6 (5%)	
node dissection not done	79	5 (6%)	
Age			
<40 yrs	63	3 (5%)	NS
40–60 yrs	95	6 (6%)	
>60 yrs	45	3 (7%)	
Received adjuvant therapy			
no	180	9 (5%)	NS
yes	23	3 (13%)	
Sex			
female	105	4 (4%)	NS
male	98	8 (8%)	

* Contiguous area including the upper *b*ack, posterior *a*rm, posterior *n*eck, and posterior *s*calp.

† Probability values were determined by the Fisher's Exact Test.[16]

of melanomas exist that metastasize early or the events leading to metastases in one melanoma subset are different from the majority of melanomas that metastasize.

The 12% frequency of regional node metastases for the BANS patients suggests that consideration be given to including these patients in future trials that test the efficacy of elective regional node dissection (ERND).

The results of the World Health Organization (WHO)[24,25] study showing inefficacy of ERND for melanoma of the distal two-thirds of the extremities should not discourage such trials in view of this study and three others[10-12] that demonstrate "subsite specificity" for the clinical behavior of melanoma even after correction for thickness. Thus, the conclusions of the WHO study for melanoma of the distal two-thirds of the extremities[24,25] may not be valid for patients with melanoma primaries in other locations.

If a randomized trial of ERND is undertaken for BANS patients, it is estimated that approximately 2500 patients in each arm of a randomized trial would be needed to prove or disprove a benefit for ERND. This number of patients was derived using the method of Armitage,[1] a statistical power exceeding 80%, an estimated probability-value of 0.05, a baseline survival rate of 80% for patients who have ERND, and a salvage rate of 4% from ERND. The 4% salvage rate was derived using the following assumptions: 1) The incidence of occult regional node metastases for BANS patients with lesions 0.76–1.69 mm in thickness in approximately 10%; 2) The five-year survival is 75% for patients with such metastases if removed electively and 35% if a wait and see policy (wide local excision only; WLE) is followed.†

The last two estimated survival rates are of course the most crucial to our argument. A detailed explanation is therefore necessary to substantiate these estimates.

Estimates of Survival for Melanoma Patients With Clinical Stage I BANS Lesions 0.76–1.69 mm in Thickness and Clinically Occult Regional Node Metastases Removed by ERND

The authors have reviewed elsewhere[9] the data from 24 studies on 468 clinical Stage I patients with clinically occult lymph node metastases found by ERND. The five-year survival rate for these 468 patients was 45%.

The multivariate analysis of prognostic factors for these patients showed that primary tumor thickness was the dominant prognostic variable and that most of the survivors had primary lesions ≤3.5 mm. The five-year disease-free survival rate was 59% for patients with lesions 0.76–3.5 mm and 17.5% for patients with lesions <3.5 mm ($p = 0.0002$). Within the 0.76–3.5 mm group, the survival rate increased with decreasing thickness. This is reaffirmed in present study by only one death among five patients with clinically occult metastases in regional lymph nodes demonstrated by ERND (five-year survival rate = 80%, Table 3).

† 10% × (0.75 − 0.35) = 0.04 = 4%.

TABLE 3. *Characteristics of the High Risk Locations (BANS) vs The Low Risk Locations (non-BANS)*

	Per Cent BANS N = 67	Per Cent non-BANS N = 136
Histologic type		
lentigo maligna melanoma	3	4
nodular melanoma	7.5	10
acral lentiginous melanoma	0	6
superficial spreading melanoma	86.5	74
indeterminate	3	5
Level of invasion		
level II	12	12
level III	64	56
level IV	24	32
level V	0	0
Histologic ulceration	19	21
Mitoses > 6/mm²	3	4
Marked lymphocytic response	31	25
Histologic regression	61	49
>1.25 mm	31	30
Microscopic satellites	7.5	4
positive nodes	6	<1
negative nodes	54	61
node dissection not done	40	38
Age		
<40 yrs	34	30
40–60 yrs	46	47
>60 yrs	20	23
Received adjuvant therapy	10	12
Sex		
female	42	57
male	58	43

Estimates of Survival for Melanoma Patients With Clinical Stage I BANS Lesions 0.76 to 1.69 mm in Thickness Who Develop Clinically Detectable Metastases in Regional Nodes After Primary Surgery

The reported overall five-year survival rates for patients who initially have no clinical evidence of metastases but who subsequently develop clinically enlarged regional nodes with metastatic melanoma are 31%,[18] 30%,[24] and 28%.[4] In contrast to patients with clinically occult regional node metastases removed by ERND for

TABLE 4. *Prognostic Model For 203 Patients With Clinical Stage I Melanoma 0.76–1.69 mm In Thickness*

Variable	Number of Patients	Number of Melanoma Deaths
Non-BANS locations	136	1 (0.7%)
BANS locations		
level II or level III	51	5 (10%)
level IV	16	6 (37.5%)

whom thickness of the primary tumor is the dominant variable,[9] primary tumor thickness has no bearing on outcome for patients with abnormally palpable pathologically involved regional nodes.[4] The authors, therefore, estimated a 35% five-year survival rate for BANS patients with lesions 0.76–1.69 mm in thickness with clinically occult regional node metastases who had such metastases removed only after becoming clinically evident.

There has been only one melanoma death among 136 patients in this series with non-BANS lesions. This death rate was not significantly different from the one death among 165 patients with clinical Stage I melanoma ≤0.75 mm in thickness who entered the authors' study over the same time period.‡ Thus, *patients with non-BANS lesions 0.76 to 1.69 mm in thickness have the same excellent prognosis as patients with lesions ≤0.75 mm in thickness and perhaps should be treated in a similar fashion.*

More than one-third of the patients with level IV BANS lesions died (Table 4). These patients may be candidates for new or promising adjuvant therapy protocols.

Nine of the 12 deaths occurred in patients with lesions ≤1.25 mm (Table 3). Thus, there was *not* a tendency for an increased proportion of deaths among patients with thicker lesions within this 0.76–1.69 mm range. This emphasizes the "quantum" behavior of thickness within the specified "natural" thickness ranges.[19]

As seen in Table 2, twice the proportion of males died as did females (*i.e.* 8 vs 4%). "Subsite" (*i.e.* BANS vs non-BANS) however, accounted for most of this difference in survival by sex. Of the 28 female BANS patients, four (14%) died. This compares with seven deaths from melanoma in 39 male BANS patients (18%). This finding is consistent with three other studies[10–12] that show *little sex difference in survival after accounting for thickness, "subsite," and clinical stage.*

‡ The one clinical stage I patient with a primary ≤0.75 mm who died in our series also had a BANS lesion.

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