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# Cutaneous Malignant Melanoma (Arizona Cancer Center Experience)

## I. Natural History and Prognostic Factors Influencing Survival in Patients With Stage I Disease

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The authors have studied the natural history of 377 patients with Stage I cutaneous malignant melanoma followed at the Arizona Cancer Center, Tucson. Two hundred eight patients, or 55%, remained free of metastatic disease after a median follow-up of 30 months. The survival at 5, 8, and 10 years was 69, 65, and 63%, respectively. Natural breakpoints in Breslow thickness for survival occurred at 0.85, 1.95, and 4.00 mm. These are not significantly different from those found by other investigators. A step-down multivariate analysis using the Cox regression model yielded four factors as highly significant in predicting survival: Breslow thickness ( $P < 0.001$ ), an age/sex interaction ( $P = 0.0012$ ), clinical ulceration ( $P = 0.0039$ ), and a prophylactic node dissection ( $P = 0.019$ ). No predictive value for a BANS or non-BANS location was detected. These results are discussed in reference to other large series which describe the natural history of cutaneous melanoma.

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A NUMBER OF INVESTIGATORS have analyzed clinical and histopathologic features of patients with Stage I malignant melanoma in order to predict survival and guide the proper treatment.<sup>1-32</sup> Important prognostic factors previously identified have included Breslow thickness,<sup>1-20</sup> Clark levels,<sup>1-3,5,7,10,14-16,20-22</sup> sex,<sup>3,5,7,8,11,13-15,17,18,20,23</sup> ulceration,<sup>3,4,7,8,10,12,14-16,19,21,24</sup> age,<sup>7,10-13</sup> location of the primary,<sup>3,7,8,10,12,13,15-17,19,20,25,26</sup> spontaneous regression of the primary,<sup>7,10,18,22</sup> satellite lesions,<sup>7,14,15</sup> histologic type of primary,<sup>5,7,8,10,16,19,21</sup> and prophylactic lymph node dissection.<sup>1,7,9,10,18,27,28</sup> Few investigators have evaluated the natural history of all patients presenting with Stage I melanoma and the prognostic factors predicting survival using univariate and multivariate statistical techniques.<sup>1,5,10,33</sup> We have analyzed the natural history of 377 patients with Stage I melanoma, and discuss in detail the prognostic factors which predict survival.

### Patients and Methods

From January 1, 1973 to April 1, 1984, 524 patients with malignant melanoma were followed at the Arizona Cancer Center, Tucson. Clinical history records were compiled from the original diagnosis (histologically proven malignant melanoma) date to the last date of follow-up or death. Staging criteria described by the international union against cancer (IUCC) classification were used.

Of the 524 patients, 440 had Stage I disease at diagnosis. Thirty-eight did not have cutaneous melanoma and were excluded. Twenty-five patients were also excluded as they did not have a wide local excision within 2 months of their diagnosis. We stipulated that the wide excision must be done within 2 months since this is the clinical time frame many patients need to confirm their diagnosis and to seek a second opinion regarding appropriate therapy. Of the 377 evaluable patients with Stage I cutaneous melanoma, 100% had their reports reviewed at our Center, whereas 191 (51%) had their initial diagnostic slides rereviewed at our center (by B.P.) for the level of involvement according to Clark,<sup>21</sup> depth of penetration in millimeters according to Breslow,<sup>1</sup> histologic type, and the presence or absence of ulceration.

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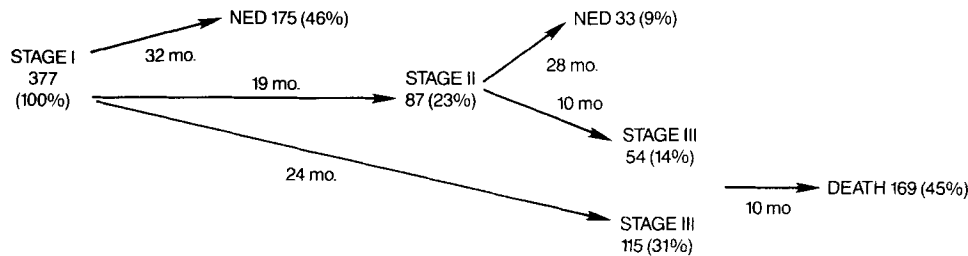


FIG. 1. Natural history of Stage I cutaneous malignant melanoma (University of Arizona Experience). NED: no evidence of disease; mo: median follow-up in months.

### Statistical Analysis

The Kaplan and Meier<sup>34</sup> method was used for statistical estimation of the survival-type curves reflecting the time from diagnosis of Stage I disease to the last date of contact or death. Methods used to compare survival-type curves included the generalized Wilcoxon method of Gehan,<sup>35</sup> the log-rank method of Mantel,<sup>36</sup> and the generalized Kruskal-Wallis method of Breslow.<sup>37</sup> Multivariate analysis of prognostic factors for survival after Stage I disease used the proportional hazard model introduced by Cox.<sup>38</sup> There were only 22 patients with a family history of melanoma, and since there were only three patient deaths, this variable was excluded from the multivariate analysis. Pathologic ulceration also was excluded from the multivariate analysis because of the high number of patients (59%) in which the status of ulceration was unknown.

## Results

### Survival History of Stage I Melanoma

The survival history of our 377 patients with Stage I cutaneous melanoma who had a surgical wide excision within 2 months of their diagnosis is summarized in Figure 1. One hundred seventy-five patients (46%) had no evidence of disease after a median time of 32 months from diagnosis. The actuarial survival at 5, 8, and 10 years was 69%, 65%, and 63%, respectively.

Eighty-seven patients of the entire group, or 23%, developed regional nodal metastases (Stage II), with a median time of 19 months. They were followed for a median time of 28 months after therapeutic lymph node dissection, and 33 (9%) have remained free of disease. The remaining 54 (14%) of the 87 patients developed distant metastases within a median time of 10 months. Thus, 208 patients (175 Stage I and 33 Stage II) or 55% remained free of metastases after a median follow-up of 30 months.

One hundred sixty-nine (45%) of all Stage I patients developed distant metastases (Stage III). The time to development of Stage III disease was 11, 29, and 55 months for the 25th, 50th, and 75th percentile, of the actuarial survival distribution. Of these patients, 54

(31%) progressed from Stage II regional metastases, whereas 115 (69%) progressed directly from Stage I to distant metastases with or without concomitant regional metastases. Patients progressed much more quickly from Stage II to Stage III (median time, 10 months) compared to those progressing from Stage I to Stage III (median time, 24 months), and this difference was highly significant ( $P < 0.001$ ). The median survival time for all patients after the development of a distant metastasis was 10 months.

### Prognostic Factors Influencing Survival

Eight clinical and four pathologic factors were evaluated retrospectively for their influence on survival in our 377 Stage I patients (Table 1). Univariate analysis demonstrated that the following features were significantly related to survival duration, with good prognosis: age younger than 50 years, presence of a lesion on an arm or leg (not involving the hand or foot), an age/sex interaction (females < 50 years), absence of clinical ulceration in the primary lesion, a thinner Breslow thickness, a shallower Clark level, a family history of melanoma, female sex, a superficial spreading melanoma, and the absence of pathologic ulceration in the primary lesion. The presence of a non-BANS lesion or a prophylactic lymph node dissection were not statistically beneficial.

A step-down multivariate analysis using the Cox regression model yielded four factors that continued to be prognostic (Table 2): a thinner Breslow thickness (vide infra), an age/sex interaction, absence of clinical ulceration, and a prophylactic node dissection. The age/sex interaction showed young women to have the best prognosis, young men and older women to have an intermediate prognosis, and older men to have the worst prognosis. Being female lost its prognostic value once the age and sex interaction was considered.

### Natural Breakpoints in Breslow Thickness for Survival

Most authors suggest that one of the most important prognostic factors in predicting regional and distant failure, as well as patient survival, is measurement of the depth of penetration of the cutaneous melanoma into the skin. Of our 377 patients with Stage I disease, 239

(63%) had Breslow thickness measurements, and 191 (80%) of these were reviewed by one pathologist (B.P.).

A stepwise analysis of patient survival as related to Breslow measurements was performed at 0.1 mm increments. Whenever the subgroup survival was altered significantly by the addition of the next 0.1 mm cohort, further determinations at 0.05 mm increments above

TABLE 1. Prognostic Factors Influencing Survival in Stage I Melanoma

	N	Median survival (mo)	Significance
<b>Clinical factors</b>			
Age			
<50	201	93	$P < 0.001^*$
≥50	176	56	
Site			
Arm/leg	101	93	$P < 0.001^\dagger$
Head/trunk	257	59	
Hand/foot	19	56	
Sex/age			
Female < 50	109	106	$P < 0.001^\dagger$
Male < 50	92	59	
Female ≥ 50	72	56	
Male ≥ 50	105	52	
Clinical ulceration			
No	221	77	$P < 0.001^*$
Unknown	94	78	
Yes	62	35	
Family history			
Melanoma	22	132	$P = 0.005^*$
No melanoma	355	69	
Sex			
Female	180	88	$P = 0.01^*$
Male	197	59	
BANS			
No	201	77	
Yes	124	60	$P = 0.17^*$
Lymph node dissection			
Yes	100	84	$P = 0.03^\ddagger$
No	239	64	$P = 0.41^\ddagger$
<b>Pathologic factors</b>			
Breslow's thickness			
≤0.75 mm	55	—	$P < 0.001^\dagger$
0.76–1.50 mm	56	91	
1.51–3.99 mm	97	72	
≥4.00 mm	31	27	
Clark's level			
I	6	—	$P < 0.001^\dagger$
II	37	95	
III	100	101	
IV	137	57	
V	24	23	
Pathologic ulceration			
No	166	92	$P = 0.02^\dagger$
Unknown	186	61	
Yes	25	39	
Type primary			
Superficial spreading	155	90	$P = 0.01^*$
Others	222	58	

\* Log-rank.

† Breslow.

‡ Wilcoxon.

TABLE 2. Favorable Prognostic Factors Predicting Survival Using Step-Down Cox Multivariate Analysis in Stage I Melanoma

Factor	Significance
Thinner Breslow thickness	$P < 0.001$
Age/sex interaction	$P = 0.0012$
No clinical ulceration	$P = 0.0039$
Prophylactic lymph node dissection	$P = 0.019$
Site (arm or leg)	NS
Female	NS
Shallower Clark's level	NS
Superficial spreading melanoma	NS
Non-BANS lesion	NS
Age	NS
Family history	NS
Pathologic ulceration	NS

NS: Nonsignificant ( $P > 0.10$ ).

and below the breakpoint were made until the most accurate and the most significant breakpoint could be determined. The first breakpoint was 0.85 mm. Subsequent analysis was done from 0.85 mm to 10.0 mm, again in 0.1-mm increments until the second breakpoint of 1.95 mm could be determined. The third breakpoint of 4.00 mm was identified in the same manner. A comparison of 5-year survivors of our 377 patients using these natural breakpoints and those described by Balch<sup>2</sup> and Day *et al.*<sup>4</sup> is shown in Table 3. There was no significant difference in 5-year survival among comparable subgroups using any of the three schema. The occurrence of Stage II and Stage III was also compared among the three schema without any significant differences. The generally accepted schema proposed by Balch, therefore, was used in establishing our subgroups for Breslow thickness during multivariate analysis.

#### *Effect of Prophylactic Lymph Node Dissection on Survival*

Of the 377 Stage I patients, 100 had a prophylactic lymph node dissection (PLND), 239 did not, and the status was unclear in 38 patients. The group undergoing a PLND had an early survival advantage ( $P = 0.03$ , Wilcoxon) and an improved median survival of 84 *versus* 64 months compared to those patients without a PLND. However, the survival curves crossed and resulted in no significant survival advantage overall ( $P = 0.37$ , log-rank).

#### Discussion

The natural history of cutaneous malignant melanoma in our 377 patients with Stage I disease who underwent a wide local excision within 2 months of their diagnosis compares quite favorably with other authors.<sup>2,3</sup> Of our patients, 46% remained free of disease

TABLE 3. Five-Year Survival of Current Study Using Breakpoints From Current Study, Balch, and Day *et al.*\*

Current study			Balch <i>et al.</i> <sup>2</sup>			Day <i>et al.</i> <sup>4</sup>		
Thickness (mm)	N	Survival	Thickness (mm)	N	Survival	Thickness (mm)	N	Survival
≤0.85	66	94%	≤0.75	55	93%	<0.85	66	94%
0.86-1.95	74	83%	0.76-1.50	56	86%	0.85-1.69	59	84%
1.96-4.00	69	72%	1.51-3.99	97	77%	1.70-3.64	80	74%
≥4.01	30	37%	>4.00	31	35%	≥3.65	34	38%

\* Survival by subgroups of patients *via* the thickness (mm) of the primary melanoma lesion according to the individual authors' natural

survival breakpoints chosen by Balch *et al.* and Day *et al.*

and 69% lived at least 5 years. These figures compare favorably to the 5-year survival of Stage I patients of 40% to 70% reported by Balch *et al.*<sup>2</sup> and Mastrangelo *et al.*, respectively.<sup>3</sup> Twenty-three percent of our Stage I patients developed Stage II disease. This finding is similar to the 15% to 23% reported by others.<sup>8,9</sup> Of the Stage II patients, 38% have remained disease free as compared to reported figures of 25% and 26%. Of the Stage I patients, 45% developed Stage III disease; a similar finding to the 24% to 36% reported by Balch *et al.*<sup>2</sup> and Mastrangelo *et al.*<sup>3</sup> We also found that the time to the development of distant metastases from initial diagnosis for the 25th, 50th, and 75th percentiles was 11, 29, and 55 months respectively. This was similar to the 16, 34, and 52 months reported by Balch and associates.<sup>29</sup>

Univariate analysis of 12 prognostic factors revealed ten factors to be favorable and highly significant and one factor to be of marginal significance (Table 1). Others also have noted these prognostic factors to be significant.<sup>1-32</sup> Multivariate analysis of all 12 prognostic factors revealed four factors to be highly significant and included Breslow thickness, age/sex interaction, absence of clinical ulceration, and a prophylactic lymph node dissection (Table 2).

The Breslow thickness was very significant ( $P = 0.0001$ ) on both univariate and multivariate analysis. The Breslow thickness has been found by many authors not only to be highly significant,<sup>1,4,5,7-10,18-20</sup> but to be

superior to Clark levels,<sup>1,5,10,16,19,33</sup> as our data also suggests. Our study confirms that Stage I patients seem to have four distinct and statistically significant subgroups when comparing the Breslow thickness with overall survival, occurrence of regional metastases, or development of distant metastases (Tables 3-5). As Breslow thickness increases, patient survival decreases. Balch and associates<sup>2</sup> have reported four subgroups of patients according to Breslow thickness that have differences in survival as well as differing rates of regional and distant metastases. The four subgroups of patients obtained are those with thicknesses of 0 to 0.75 mm, 0.76 to 1.50 mm, 1.51 to 3.99 mm, and ≥ 4.00 mm. Recently, Day *et al.*<sup>4</sup> also have reported survival differences in four slightly different Breslow thickness subgroups.

As shown in Table 3, there were no significant differences between stratification of our 377 patients *via* three slightly different natural breakpoints, and reports by Balch *et al.*,<sup>10</sup> and Day *et al.*<sup>4,6</sup> As shown in Table 4, there were no significant differences in the 5-year survival of our 377 patients compared with the 1152 patients reported by Veronesi<sup>8</sup> and the 155 patients reported by Balch and co-workers.<sup>2</sup> The frequency of progression to Stage II within 3 years in our patients was slightly lower than those of Balch *et al.* (Table 5). However, unlike his study, it is our clinical experience, and that reported by Veronesi,<sup>8</sup> that there are a small number of patients with 0.75 mm lesions who progress to nodal or distant metastases. The progression to Stage III

TABLE 4. Comparison of 5-Year Survival Using Breslow Thickness

Thickness (mm)	Current		Veronesi <sup>8</sup>		Balch <i>et al.</i> <sup>2</sup>	
	N	5-yr survival	N	5-yr survival	N	5-yr survival
≤0.75	55	93%	107	95%	38	100%
0.76-1.50	56	86%	185	82%	40	64%
1.51-3.99	97	77%	572*	65%	56	68%
≥4.00	31	35%	288†	38%	22	34%

\* Thickness 1.51-4.50 mm.

† Thickness ≥ 4.50 mm.

TABLE 5. Frequency of Progression to Stage II and Stage III as Determined by Breslow Thickness

Thickness (mm)	Current study			Balch <i>et al.</i> <sup>2</sup>		
	N	3-yr Stage II	5-yr Stage III	N	3-yr Stage II	5-yr Stage III
≤0.75	55	9%	11%	38	0%	0%
0.76-1.50	56	13%	21%	39	25%	19%
1.51-3.99	97	24%	26%	57	57%	35%
≥4.00	31	39%	74%	22	62%	76%

within 5 years was quite comparable between our group of patients and those of Balch *et al.*<sup>2</sup>

Younger patients (<50 years old) did better ( $P < 0.001$ ) on univariate analysis, an observation noted by others.<sup>7,10-13</sup> Women also did better than men on univariate analysis ( $P = 0.01$ ), a parameter which has been noted by others on univariate<sup>3,5,7,8,11,13-15,17,18,20,23</sup> and multivariate analysis.<sup>5,20</sup> Multivariate analysis of our prognostic factors in patients showed that the age/sex interaction variable replaced age and sex as a prognostic factor. Our study suggests a markedly better prognosis for young women and a poorer prognosis for men and older women on both univariate ( $P < 0.001$ ) and multivariate analysis ( $P = 0.002$ ). Similar results also have been noted by Davis *et al.*<sup>13</sup>

Pathologic and clinical ulceration were significant on univariate analysis ( $P = 0.02$  and  $P < 0.001$ , respectively) and clinical ulceration remained significant on multivariate analysis ( $P = 0.0039$ ). Others also have recorded the importance of ulceration, using either univariate<sup>9,11,13,15,16</sup> or multivariate analyses.<sup>4,5,11,20,22,29</sup>

A family history of melanoma was shown to be highly favorable ( $P = 0.005$ ) on univariate analysis. Although this was excluded from multivariate analysis because of its uncommon occurrence, many studies support its importance. Before the dysplastic nevus syndrome had been described, patients with multiple primaries had been shown to have a better prognosis independent of the thickness of the lesion.<sup>8</sup> The natural history of the B-K mole syndrome, the dysplastic nevus syndrome, and of patients with multiple primaries currently is under clinical study.<sup>30-32</sup>

The site of the primary melanoma was significant on univariate analysis ( $P < 0.001$ ) but had no significance on multivariate analysis. Primary site has also been shown by others to be significant on univariate and lose its prognostic significance on multivariate analysis.<sup>9,14,16,18,19,21-23,25,26,36</sup> Also noted to be important on univariate analysis was the presence of the superficial spreading variant rather than another primary type ( $P = 0.01$ ). This fact offered no additional prognostic information after knowing the thickness and location of the primary melanoma, and the age and sex of the patient. The loss of the prognostic significance of the primary type on multivariate analysis has been widely reported.<sup>5,7,8,10,16,19,22</sup>

Prophylactic lymph node dissections have been the subject of controversy for years. Some retrospective studies<sup>2,15,16,32,39</sup> have shown benefit in certain subgroups, whereas a large prospective study in patients with only extremity lesions has failed to show a benefit.<sup>18</sup> Our study showed that patients undergoing a

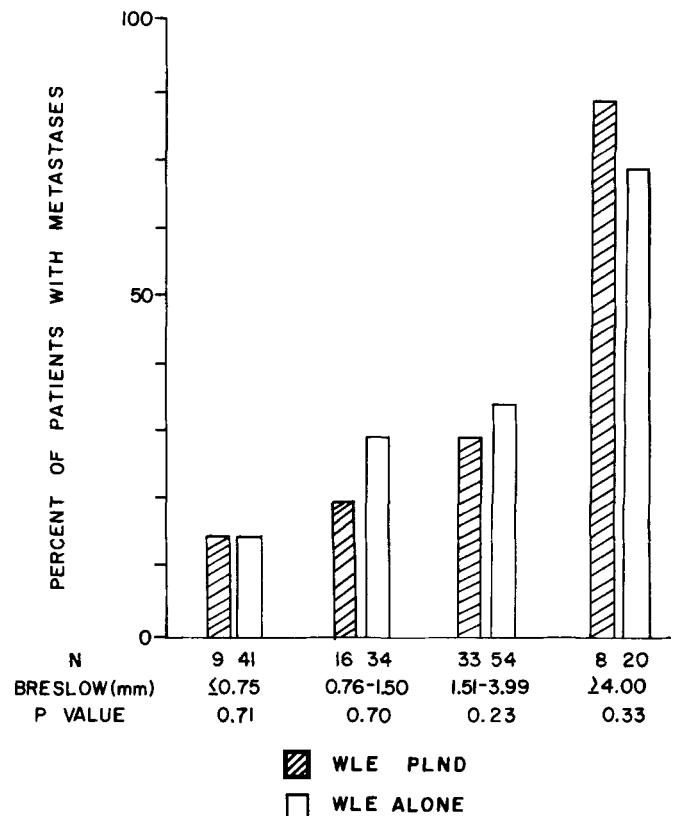


FIG. 2. Five-year incidence of Stage I disease of regional node metastases with or without prophylactic lymph node dissection.

PLND did significantly better initially (Wilcoxon,  $P = 0.03$ ) but failed to show any benefit as time progressed (log-rank,  $P = 0.37$ ). However, on multivariate analysis, patients who had had a PLND did markedly better ( $P = 0.019$ ). Does any subset of patients benefit from a prophylactic lymph node dissection?

Balch *et al.*<sup>2</sup> have reported that patients with lesions 1.50 to 3.99 mm thick have a decreased incidence of distant metastases and improved overall survival if a PLND is done in addition to a wide local excision (WLE). Of our 239 Stage I patients with known Breslow thickness, 149 patients underwent WLE alone, 66 underwent WLE + PLND, and in 24 patients with WLE, the PLND was unknown. An analysis of our 215 patients (149 patients with WLE alone were compared to 66 patients with WLE + PLND) was performed. After WLE + PLND, patients with lesions 1.51 to 3.99 mm thick had a more marked reduction (17%) in the incidence of developing regional nodal metastases than those with WLE alone (46%) (Fig. 2,  $P = 0.012$ ). Patients with WLE + PLND were stratified by Breslow thickness into four subgroups. There was no statistically signifi-

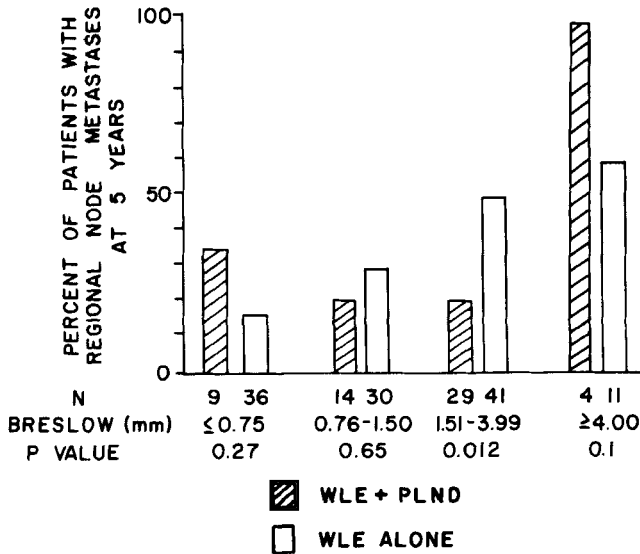


FIG. 3. Five-year incidence of distant metastases of Stage I disease with or without prophylactic lymph node dissection stratified by Breslow thickness.

cant reduction in the incidence of distant metastases (Fig. 3) or a survival advantage in those patients who underwent a PLND (Fig. 4).

As shown in Table 6, our patients showed no statistically significant survival benefit from PLND in any Breslow thickness subgroup. Our results do not support the results of the study by Balch *et al.*<sup>2</sup> in which he found that a PLND increased survival from 58% to 94% in the

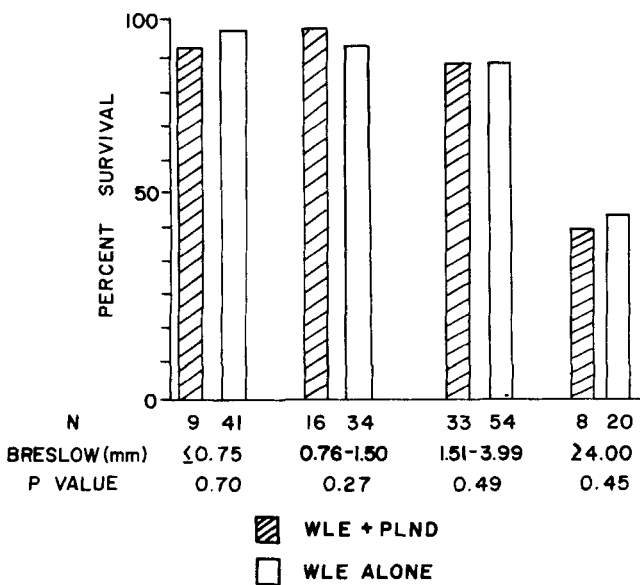


FIG. 4. Five-year survival of Stage I disease with or without prophylactic lymph node dissection (PLND) stratified by Breslow thickness.

TABLE 6. Five-Year Survival in Patients With or Without Prophylactic Lymph Node Dissection Stratified by Breslow Thickness

Thickness (mm)	Current study			Balch <i>et al.</i> <sup>2</sup>		
	N	WLE alone	PLND	N	WLE alone	PLND
≤0.75	50	93%	89%	58	100%	100%
0.76-1.50	50	82%	94%	40	58%	94%
1.51-3.99	87	72%	75%	56	37%	83%
≥4.00	28	40%	36%	22	30%	40%

WLE: wide local excision; PLND: prophylactic lymph node dissection.

0.76 to 1.50 mm group ( $P = 0.04$ ) and from 37% to 83% in the 1.51 to 3.99 mm group ( $P = 0.01$ ). The 5-year survival of Balch *et al.*<sup>2</sup> of 58% in their WLE group of 0.76 to 1.50 mm is very low (82% in our patients, and from 70%–82% as reported by Breslow,<sup>1</sup> Kapelanski,<sup>27</sup> and Veronesi<sup>8</sup>). For the 1.51 to 3.99 mm subgroup, our overall 5-year survival of 73% and the overall 5-year survival of Balch *et al.*<sup>2</sup> of 68% are quite close to the 65% survival reported by Veronesi.<sup>8</sup> However, there may be some type of patient selection differences between our two groups since our patients with WLE alone ( $N = 54$ ) did significantly better (72% 5-year survival) compared to the WLE alone group ( $N = 18$ ) of Balch *et al.*<sup>2</sup> with a 37% 5-year survival.

Veronesi *et al.*,<sup>28</sup> in a large clinical trial, reported that there was no statistical survival benefit in a prospective trial of WLE versus WLE + PLND in patients with lesions on the extremity. Critics of this trial point to the large proportion of women in the study who may have had a better prognosis, the trend ( $P = 0.13$ ) of better survival in those patients with 3.0 to 3.9 mm thick lesions undergoing WLE + PLND, and the difficulty of detecting statistical significance since extremity lesions have the best prognosis. It is clear that the effect of a PLND for subgroups of patients with different Breslow thicknesses requires further investigation.

The results reported by Day *et al.*<sup>19</sup> for BANS and non-BANS lesions and our results differ in several areas (Table 7). Their 8-year survival of 99% for all patients with lesions < 0.85 mm is high compared with the 87% 8-year survival of our patients and the 89% reported by Veronesi.<sup>8</sup> Their 99% 8-year survival in patients with non-BANS lesions 0.85 to 1.69 mm thick is high when compared to our 82% survival. The 93% 8-year survival for all patients with lesions 0.85 to 1.69 mm thick also is high when compared to our 82% survival, the 82% survival reported by Veronesi,<sup>8</sup> the 70% 5-year survival reported by Breslow,<sup>1</sup> and the 64% 5-year survival reported by Balch *et al.*<sup>2</sup> Our series does not support the

TABLE 7. Eight-Year Survival by Thickness and BANS or Non-BANS Location

Thickness (mm)	Veronesi <sup>8</sup>	Day <i>et al.</i> <sup>6</sup>		Current study			Significance <sup>§</sup>	
	Total	Non-BANS	BANS	Total	Non-BANS	BANS		Total*
<0.85	89%	99%	99%	99%	89%	82%	87%	0.45
0.85-1.69	82%	99%	80%	93%	82%	81%	82%	0.93†
1.70-3.64	<60%	—	—	69%	73%	71%	75%	0.91
≥3.65	>35%‡	—	—	38%	31%	31%	36%	0.79‡

\* Total in the group of the current study equals BANS + non-BANS + unknowns.

† 1.51-3.00 mm group.

‡ >4.51 mm group.

§ Significance of BANS *versus* non-BANS in the current study.

tenet that there is prognostic survival significance of BANS *versus* non-BANS lesions, even when differences in Breslow thickness are considered. Although greater than 50% of patients with Stage I melanoma patients remained free of disease, almost 50% progressed with distant metastases.

A knowledge of the natural history of patients with Stage I melanoma can be quite helpful in assessing which prognostic factors are predictors for prolonging patient survival. When evaluating survival of subgroups of patients using Breslow thickness, our natural break-points were not shown to be significantly different from those derived by Breslow, Balch *et al.*<sup>2</sup> or Day *et al.*<sup>4,6</sup> Therefore, our data support the usage of those subgroups described by Balch *et al.*<sup>2</sup> and Breslow as a standard reference. Multivariate analysis revealed four highly significant prognostic variables for predicting survival: thinner Breslow thickness, an age/sex interaction, absence of clinical ulceration, and a prophylactic lymph node dissection. The use of this information will continue to help us in the assessment of the natural history of cutaneous melanoma and biological features underlying the clinical variability of the disease.<sup>40</sup>

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