Cutaneous Malignant Melanoma

II. The Natural History and Prognostic Factors Influencing the Development of Stage II Disease

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The survival history of 259 patients with Stage I cutaneous malignant melanoma who were at risk for developing regional nodal metastases (Stage II) were studied. Eighty-seven of 377 Stage I patients (23%) developed regional nodal metastases (Stage IIb) with a 40% 5-year survival. Fifty patients had regional nodal metastases at presentation, with or without a known primary (Stages IIa or IIc, respectively), with a 42% 5-year survival. A step-down multivariate analysis using the Cox regression model revealed four risk factors as being highly significant for predicting a more favorable survival outcome: (1) thinner Breslow thickness \( (P = 0.0001) \), (2) pathologic Stage I disease \( (P = 0.004) \), (3) no clinical ulceration \( (P = 0.0004) \), and (4) being a woman younger than 50 years of age \( (P = 0.029) \). These results are discussed in reference to other series.


Increasing knowledge of the natural history of patients with Stage I cutaneous melanoma has led to a greater understanding of the disease and its treatment. Development of regional and distant metastases occurs at a higher incidence as the primary lesions became more advanced, i.e., more invasive (Clark level), thinner (Breslow thickness), and/or ulcerated. Patients with lesions less than 0.75 mm thickness need only a wide local excision for curative treatment. However, the proper surgical management for patients with lesions \( \geq 0.76 \) mm (wide local excision with or without a prophylactic lymph node dissection) remains unclear.

A better understanding of the natural history of patients with Stage I disease has allowed less aggressive treatment of those with a good prognosis (Breslow thickness \( \leq 1.50 \) mm), thereby saving the complications of an unnecessary regional approach. In patients with an intermediate prognosis (1.51 to 3.99 mm), a more aggressive regional treatment approach may prevent subsequent nodal and distant metastases, and improve the disease-free interval and/or survival. In patients with a worse prognosis and high probability of distant metastases (>4.00 mm), a less aggressive regional approach may not be indicated.

A multivariate analysis of 11 prognostic variables in 259 Stage I melanoma patients at risk for developing Stage II disease revealed the following four risk factors as significant for predicting a more favorable outcome: (1) thinner Breslow thickness \( (P = 0.0001) \), (2) pathologic Stage I disease \( (P = 0.004) \), (3) no clinical ulceration \( (P = 0.0004) \), and (4) a woman younger than 50 years of age \( (P = 0.029) \).

Patients and Methods

Patient Population

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

Of the 524 patients, 440 patients had Stage I and 54 patients had Stage II disease at diagnosis. Thirty-eight patients with Stage I noncutaneous melanoma were excluded from analysis. Twenty-eight patients who did not have a wide local excision within 2 months were also excluded, leaving 374 patients who had adequate surgical therapy.
for Stage I cutaneous melanoma. To evaluate prognostic factors that could predict which patients with Stage I melanoma developed local nodal metastases (Stage II), 115 patients who progressed directly from Stage I to Stage III (distant metastatic disease) were also excluded.

The history of disease recurrence of the 259 evaluable patients diagnosed as Stage I is summarized in Figure 1. The median follow-up was 30 months. Of the 259 evaluable patients, 158 (61%) had their initial diagnostic slides reviewed by one of the authors (B.P.) for the level of penetration according to Clark et al., depth of penetration in millimeters, according to Breslow, histologic type, and the presence or absence of ulceration. The natural history of the patients who developed Stage II disease is also summarized in Figure 1. Eighty-seven (34%) of the 259 patients developed pathologic Stage II disease (delayed nodal metastases, Stage IIb) at a median follow-up of 19 months, whereas 172 patients (median follow-up of 33 months) remained free of disease.

Of the 54 patients with Stage II disease at diagnosis (initial Stage II disease [Stage IIa and IIc]), two patients with noncutaneous melanoma and two patients who did not have a regional lymph node dissection within 2 months of their diagnosis were excluded from subsequent analysis, leaving 50 evaluable patients. Their median follow-up was 25 months.

Thus, 87 (64%) of the evaluable patients with Stage II disease progressed from Stage I melanoma and 50 (36%) initially had Stage II disease. All patients with nodal disease underwent a surgical lymphadenectomy and were shown to have metastatic involvement of regional lymph nodes confirmed by a pathologist. Removal of the primary tumor by a wide local excision was done if the patients also had a primary lesion.

Statistical Analysis

The Kaplan and Meier method was used for statistical estimation of the survival-type curves reflecting the time from Stage I diagnosis to the last date of contact or death. Methods used to compare survival-type curves were the generalized Wilcoxon method of Gehan, the log-rank method of Mantel, and the generalized Kruskal-Wallis method of Breslow. Multivariate analysis of prognostic factors for regional recurrence after Stage I disease used the 6X proportional hazard model.
Eighty-seven patients (63%) developed Stage II disease subsequent to documented antecedent Stage I melanoma (delayed nodal metastases or Stage IIc). Thirty-three of those (38%) were alive without evidence of melanoma after a median time of 28 months. Fifty-four (62%) had progressed to Stage III disease after a median time of only 10 months; two (4%) of those were alive, and 52 (96%) had died with a median time of 17 months. Their 5-year survival was 40%.

Fifty patients (36%) developed Stage II disease, de novo, i.e., without an antecedent cutaneous lesion. Of these, 36 had synchronous nodal metastases (Stage IIa) and 14 had nodal metastases without a known primary (Stage IIc). Of these 50 patients, 21 (42%) were free of disease after a median follow-up of 27 months, three (6%) were alive with Stage III disease, and 26 (52%) had died of Stage III disease, after a median time of 18 months. The 5-year survival of the 36 Stage IIa patients was 42%. Of these, 13 (36%) were NED after a median follow-up of 27 months, two (6%) were alive with Stage III disease, and 21 (58%) had died of Stage III disease, with a median time of 17 months.

The 5-year overall survival of the 14 Stage IIc patients was 64%. Eight patients (57%) were alive with no evidence of melanoma. After a median follow-up of 30 months, one patient (7%) was alive with Stage III disease. Five patients (36%) had died of Stage III disease after a median follow-up of 21 months.

When comparing the remission rates and 5-year survival rates of the various Stage II groups of patients, there were no statistically significant differences.

Predicting the Development of Nodal Metastases

Results from a univariate analysis of eight clinical and four pathologic prognostic factors are shown in Table 1. The nine factors that predicted a greater median time to occurrence of nodal metastases were as follows: no clinical ulceration; an age/sex interaction, with young women doing much better than men or older women; thinner Breslow thickness; shallower Clark’s level; superficial spreading primary type, no pathologic ulceration; female gender; age younger than 50 years; and a negative lymph node dissection revealing no nodal disease (pathologic Stage I). A family history of melanoma was of borderline significance (P = 0.06). The site of the primary and the location of the primary at a BANS (upper back, posterior arm, posterior neck, or posterior scalp)13 versus non-BANS site was not prognostic.

The results of multivariate analysis using a Cox proportional hazard model of the 11 prognostic variables are shown in Table 2. Highly significant for predicting a more favorable outcome (less risk for developing nodal metastases) were a thinner Breslow thickness (P = 0.0001), negative lymph node dissection (pathologic Stage I, P

### Table 1. Univariate Analysis of Prognostic Factors Influencing the Development of Nodal Metastases (Stage II) in Melanoma

<table>
<thead>
<tr>
<th>Clinical factors</th>
<th>N</th>
<th>Median survival (mo)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Ulceration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>160</td>
<td>114</td>
<td>P &lt; 0.001*</td>
</tr>
<tr>
<td>Unknown</td>
<td>59</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td><strong>Age/Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female &lt; 50</td>
<td>74</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Male &lt; 50</td>
<td>64</td>
<td>65</td>
<td>P &lt; 0.001*</td>
</tr>
<tr>
<td>Female ≥ 50</td>
<td>49</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Male ≥ 50</td>
<td>72</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>123</td>
<td>91</td>
<td>P = 0.005†</td>
</tr>
<tr>
<td>Male</td>
<td>136</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td><strong>Breslow’s thickness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.75 mm</td>
<td>50</td>
<td>—</td>
<td>P = 0.17*</td>
</tr>
<tr>
<td>0.76-1.50 mm</td>
<td>49</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>1.51-3.99 mm</td>
<td>80</td>
<td>6</td>
<td>P &lt; 0.001*</td>
</tr>
<tr>
<td>≥ 4.00 mm</td>
<td>18</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Clark’s Level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>33</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>85</td>
<td>105</td>
<td>P &lt; 0.001*</td>
</tr>
<tr>
<td>IV</td>
<td>101</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>11</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td><strong>Type primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>129</td>
<td>108</td>
<td>P &lt; 0.001*</td>
</tr>
<tr>
<td>Others</td>
<td>130</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td><strong>Pathologic ulceration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>138</td>
<td>97</td>
<td>P &lt; 0.001*</td>
</tr>
<tr>
<td>Unknown</td>
<td>101</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>12</td>
<td></td>
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</tbody>
</table>

* Breslow. † Log-rank.

### Results

#### Natural History

Of the 137 total patients with Stage II disease, 54 (39%) had no evidence of disease (NED) after a median follow-up of 27 months. Eighty-three (61%) progressed to Stage III disease, and of those, five (6%) were alive with Stage III disease and 78 (94%) had died from Stage III disease, with a median time of 19 months. The overall 5-year survival was 44%.
The age/sex interaction also revealed significant differences, with young women having the most favorable prognosis; only 1% developed Stage I disease, whereas older women or men had the least favorable prognosis and 35% developed Stage II disease. The incidence of Stage II disease for patients with superficial spreading melanoma was 18% versus 39% for patients with other primary types.

The natural history of our 137 patients with cutaneous pathologic Stage II melanoma is similar to that reported by others. Eighty-seven (23%) of our 374 patients with Stage I melanoma developed Stage II disease. This compares with the 15%, 23%, and 32% reported in the studies of Balch et al., De Vita and Fischer, and Eastwood and Bakler, respectively. The median time to developing Stage II disease was 19 months, similar to the 13 months reported by Eastwood and Bakler and the 16 months by Balch et al. Although Balch et al. reported an equal number of Stage II A (44%) and Stage II B (44%) patients, we noted a slightly higher proportion of Stage II B patients, (64% versus 26%). Stage II C patients were uncommon in the current study (10%), as well as in studies by Balch et al. (12%) and Callery et al. (7%).

Discussion
Distant metastases developed in 61% of our patients with a median time of 19 months. This figure is similar to the 72% incidence of distant metastases with a median time of 16 months reported by Balch et al. The overall 5-year survival of our Stage II patients was 44% and is within the range of figures reported by others (29% to 51%). Stage II A and II B patients had equivalent 5-year survival rates from their date of nodal involvement (40% and 42%, respectively). Although the 28% overall 5-year survival of Balch et al. is slightly lower than the 41% noted in our study, they found that Stage II A and II B patients had equivalent survival rates at 5 and 10 years. Stage II C patients seemed to do better than other Stage II patients, with a 5-year survival of 64% (versus 41% for Stage II A plus II B). This finding was not statistically significant because of the small number of patients. A higher 5-year survival in Stage II C patients was also noted by Balch et al. but could not be definitively substantiated because of the small number of patients in our series.

A number of authors have quantitated survival after Stage I disease, whereas only a few authors have studied survival after Stage II disease. Many authors have confirmed the increasing occurrence of Stage II disease with increasing thickness of the primary melanoma. However, only Eastwood and Bakle reported a multivariate analysis that predicts the occurrence of regional nodal metastases in patients with Stage I disease.

Our univariate analysis showed that nine prognostic factors were important and one factor was marginally significant in predicting Stage II disease (Table 1). Four factors were highly significant and one factor marginally significant after multivariate analysis (Table 2). A thinner Breslow thickness was significant both on univariate (P < 0.001) and multivariate analysis (P = 0.0001) and was the most important prognostic factor. A thinner Breslow thickness has been shown to predict both a better survival after Stage I disease, as well as to predict a lower frequency of nodal metastases using either univariate or multivariate analysis.

Pathologic stage (as determined by a PLND) was the second most important prognostic factor and was highly significant on both univariate (P < 0.001) and multivariate (P = 0.002) analyses. Pathologic Stage I patients have no lymph node involvement at the time of surgery, whereas clinical Stage I patients have an increased risk of clinically undetectable but pathologically proven nodal metastases as the thickness of their primary increases. Thus, a patient with clinical Stage I disease has a poorer prognosis than a patient with pathologic Stage I disease. As shown in Figure 2, patients with a primary lesion 1.51 to 3.99 mm thick had a significantly lower frequency of regional nodal metastases at 5 years (17% versus 46%) if they underwent a PLND and were confirmed as having pathologic Stage I disease (P = 0.012). These results support the recommendations of Balch et al. that patients with lesions 1.50 to 3.99 mm thick should undergo a PLND. Balch et al. did not comment on the development of Stage II disease after a PLND. However, a 46% increase in 5-year survival (from 37% to 83%) was noted in the subgroup of patients with lesions with Breslow thickness of 1.51 to 3.99 mm. Our multivariate analysis confirmed the better prognosis of Stage I patients undergoing a PLND (P = 0.019). Patients who were upstaged to pathologic Stage II A had no differences in 5-year disease-free survival, frequency to developing distant metastases, or overall 5-year survival when compared to those with delayed nodal metastases (Stage II B). Therefore, patients with lesions 1.51 to 3.99 mm in thickness that underwent a PLND had a significantly lower frequency of developing nodal metastases if no nodal metastases were present at the time of surgery. However, if delayed nodal metastases did occur, these Stage II B patients had the same 5-year survival from the time of nodal metastases development and the same frequency of developing distant metastases as did Stage II A patients (once nodal metastases occurred, Stage II A and II B patients acted similarly).

The overall incidence of developing regional nodal metastases according to Breslow thickness was as follows: ≤0.75 mm = 11%, 0.76 to 1.50 mm = 18%, 1.51 to 3.99 mm = 34%, and ≥4.00 mm = 67%. The 11% incidence of Stage II disease at 5 years in patients with ≤0.75 mm lesion is high compared to the results of Balch et al. and Breslow (9%), but is similar to that of Cohen et al. (9%). Veronesi reported a 5-year death rate of 5% in patients with lesions ≤0.75 mm. Our 18% incidence of Stage II disease in the 0.76 to 1.50 mm subgroup is similar to the 23% to 33% reported by Balch et al. and Breslow. The 0.76 to 1.50 mm subgroup has an intermediate prognosis between the ≤0.75 mm and 1.51 to 3.99 mm subgroups, as has been confirmed by Breslow, Veronesi, and Balch et al. The 34% incidence of Stage II disease in the 1.51 to 3.99 mm subgroup was slightly lower than the 57% incidence seen at 3 years by Balch et al. The 67% incidence of Stage II disease of the ≥4.00 mm subgroup is consistent with the 65% reported by others and the 38% 5-year survival reported by Veronesi. Thus, the subgroup of patients with 1.51 to 3.99 mm thick lesions tend to be at high risk for nodal metastases and may benefit from a PLND.

Absence of clinical ulceration was highly significant both on univariate (P < 0.001) and multivariate analysis (P = 0.004). Although pathologic ulceration was also highly significant on univariate analysis (P < 0.001), it was not significant (P > 0.10) on multivariate analysis after considering the significance of clinical ulceration, Breslow thickness, and primary type (increased incidence in nodular melanomas). Ulceration has been shown to be an independent
risk factor in Stage I melanoma, predicting a shorter survival with an increased risk of nodal and distant metastases, as noted also by others on univariate \(^5\) and multivariate \(^4,7,8,15,16,31,41\) analyses.

By univariate analysis, women and patients younger than 50 years had less risk of developing Stage II disease \((P < 0.005\) and \(P = 0.01\), respectively). An age/sex interaction was highly significant on univariate \((P < 0.001)\) analysis and remained significant \((P = 0.029)\) on multivariate analysis, and replaced age and sex as prognostic factors. Younger patients are reported to have an improved survival in Stage I disease. \(^7,9,30,41\) Women have also had an improved survival in Stage I disease on both univariate \(^5,8,9,14,29-31,34,41\) and multivariate \(^11,14,41\) analyses. An age/sex interaction with improved survival for young women has been previously reported in Stage I patients by Davis et al. \(^12\) and Meyskens et al. \(^41\) This interaction was noted to replace both age and sex as prognostic factors in predicting nodal metastases on multivariate analysis. There was a markedly better prognosis for young women and a poorer prognosis for young men followed by older women; prognosis was poorest for older men.

A patient with a superficial spreading melanoma had less risk of developing Stage II disease than did a patient with another type of primary (nodular or acral) on univariate analysis \((P < 0.001)\). Even though there was a significance of \(P = 0.039\) on multivariate analysis, the type of primary could be removed from the Cox model without significantly altering the model. The type of primary was therefore considered to have marginal significance. Previous multivariate analyses in Stage I patients have also failed to show that the type of primary has had any prognostic significance. \(^4,5,14,31,35,41\)

Although Clark's level was highly significant on univariate analysis \((P < 0.001)\), it was not significant on multivariate analysis because its prognostic importance was replaced by the Breslow thickness. This finding has also been documented in Stage I patients by others. \(^4,5,14,29,40,41\)

A family history of melanoma showed a marginal significance on univariate analysis. Although family history of melanoma was excluded from multivariate analysis because of its uncommon occurrence, many studies support its importance. \(^36-38\) 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. \(^5\) The natural history of the dysplastic nevus syndrome and of patients with multiple primaries is currently under clinical study. \(^36-38\)

The primary site did not have significant prognostic importance on both univariate and multivariate analysis. Although Stage I patients with extremity lesions have a better prognosis than do patients with head, trunk, hand, or foot lesions on univariate analysis, \(^4,5,7,8,12,16,31-34,41\) site has moderate \(^4\) or no significance \(^5,7,8,14,41\) on multivariate analysis. Although BANS lesions have been reported to have prognostic significance in a subgroup of Stage I patients, \(^28,35\) it has not had this significance for Stage I patients as a whole. \(^28,41\)

A recent multivariate analysis reported by Eastwood and Baker \(^22\) demonstrated six of 19 histologic risk factors as predictive of nodal metastases. Our results are similar in that the thickness of the lesion and sex of the patient were highly significant. However, they found age not to be prognostic, and no age/sex interaction was analyzed. A major difference in their study is the absence of any prognostic significance on univariate analysis of the cell type, Clark levels, or pathologic versus clinical stage of patients. We cannot comment on the prognostic significance of tumor elevation, mitotic activity, pleomorphism, or host reaction because this was not addressed in our study. However, Veronesi et al. \(^14\) reported that these variables were not important in predicting survival of Stage I patients on multivariate analysis.

Only 87 of 374 patients (23%) with Stage I melanoma who progressed to pathologic Stage II melanoma were at risk for developing regional metastases. However, it is important to predict which patients are at highest risk for Stage II progression so that new treatments may be developed to prevent recurrence. The eventual progression of 61% of these patients to Stage III disease and a short survival underscores this importance. Even if local nodal metastases occur in patients with melanoma (Stage II), a relatively high proportion of patients (40%) remained free of disease after undergoing a lymph node dissection.

REFERENCES


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**Erratum**

A correction should be noted in the article, "Cutaneous Malignant Melanoma (Arizona Cancer Center Experience): 1. Natural History and Prognostic Factors Influencing Survival in Patients With Stage I Disease," by Meykens et al. (Cancer 1988; 62; 1207-1214). Although the bar graphs for Figures 2 and 3 are correct, the figure legends for the figures were reversed. Figure 2 on page 1211 corresponds with the legend assigned to Figure 3 on page 1212; Figure 3 corresponds with the legend assigned to Figure 2.