Factors Prognostic for Survival in Patients with Malignant Melanoma Spread to the Regional Lymph Nodes

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To establish clinical and histologic determinants of survival, records of all UCLA patients with resectable melanoma metastatic to the lymph nodes during the years 1954–1976 were reviewed. These 150 patients were treated first with wide excision, lymphadenectomy, and with radiation/chemotherapy and/or additional surgery only if further recurrences developed. None received adjuvant immunotherapy or chemotherapy. In 97 of 139 patients with identified primary tumors, slides of the primary lesion were reviewed. Putative prognostic factors included age, sex, parity, site of primary tumor, presence of satellitosis, clinical status of nodes, histologic characteristics of primary lesion (Clark's level, thickness of tumor, presence/width of ulceration, and number of mitoses/HPF), time from biopsy of primary tumor to lymphadenectomy, and number of positive nodes. Kaplan–Meier estimates of survival for the entire group at one, two, five, and ten years were 73, 55, 37, and 33%, respectively. Median follow-up period of *survivors* was four years. Univariate analyses using the log-rank test showed that thickness of the primary lesion ($p < 0.001$), width of ulceration ($p = 0.003$), absence of ulceration ($p = 0.024$), and number of positive nodes ($p = 0.033$) were prognostic for survival. In multivariate analysis by the Cox procedure, thickness of the primary ($p = 0.001$) and number of melanoma-containing nodes ($p = 0.043$) were prognostic for survival. Location of the primary tumor became marginally significant ($p = 0.12$) in the multivariate model. These findings demonstrate the prognostic importance of characteristics of both the primary lesion and extent of regional dissemination. Future prospective randomized trials for (adjuvant) therapy of Stage II melanoma should be stratified by these variables.

THE FIVE-YEAR SURVIVAL RATE for patients with malignant melanoma localized to the primary site varies from 75 to 90%.[8,13] For patients with tumor spread to the regional lymph nodes (Stage II), the comparable figure varies from 14 to 51%.[1,8,13,17] Since Stage II patients are likely to develop further recurrences and die from their extended disease, they are candidates for experimental cytotoxic chemotherapeutic or immunologic adjuvant therapy in prospective randomized trials. To maximize the validity of such trials, the patient population examined should be as homogeneous as possible, and patients should be stratified according to those factors most important for their stage of disease. The nature and relative importance of such prognostic factors are best determined for each study population by multivariate statistical analysis.

This study assessed the effect on survival of histologic and clinical features in 150 Stage II melanoma patients. These patients had been treated by lymphadenectomy, but had received neither chemotherapy nor immunotherapy after lymphadenectomy prior to their developing further detectable disease. These individuals are representative of the type of patients that would constitute a Stage II adjuvant therapy protocol, and their clinical course up to the point of development of post-lymphadenectomy metastases represents the "natural history" of such patients treated by surgery alone.

Patient and Methods

Clinical records of all melanoma patients with histologically proven regional lymph node metastases (Stage II) seen at the UCLA Center for the Health Sciences between January 1954 and June 1976 were reviewed. Patients were excluded if unresectable soft tissue invasion was observed at lymphadenectomy (as documented in the operative or pathology reports), if they had disseminated melanoma present at the time of lymphadenectomy, or if they had received prophy-

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lactic immunotherapy or chemotherapy following lymphadenectomy. Presence of satellitosis and/or intransit metastases were not exclusion criteria. Patients who had presented initially with localized melanoma were eligible for the study if they were subsequently seen at UCLA when nodal disease developed, provided that nodal disease was diagnosed before systemic involvement. If, after node dissection, melanoma metastasized beyond the regional nodes (Stage III disease), patients were treated with chemotherapy, radiation therapy, immunotherapy, or further surgery. There were 150 such Stage II patients, aged 14 to 79 years (median 48 years), including 90 males and 60 females. These patients represent the 22-year UCLA experience with melanoma patients treated for Stage II disease by surgery alone without systemic adjuvant therapy.

The following clinical and histologic data were collected from patient charts, local physicians, the patients and their relatives: demographic data, location and gross description of the primary lesion, treatment of the primary lesion and associated complications, clinical assessment of lymph nodes, chronology of progression of disease and of therapy, timing and extent of complications of lymphadenectomy, and clinical or autopsy status at last follow-up or death. Histologic slides of the primary melanoma were available for 97 (70%) of the 139 patients who had identifiable primary tumors. Eleven patients had regional nodal metastases without identifiable primary malignant melanomas (occult primaries, 7%).

The histologic evaluation was made in a "blind" fashion by one pathologist (AJC), who at the time of examining the slides had no knowledge of the patient's clinical course. The 97 patients with available histologic material had the primary nature of the tumor confirmed. The histologic features recorded were the tumor profile,[22] the presence and micrometer-measured width of ulceration,[2] the histogenetic pattern,[24] the level of invasion,[7] the tumor thickness as measured by micrometer,[4-6,15] the presence or absence of lymphatic or blood vascular invasion, the mitotic rate using the intervals established by McGovern et al.,[24] and the extent of any associated lymphoreticular infiltrate. After the histologic evaluation had been completed, 10% of the histologic slides were coded and re-reviewed by the same observer. The results of the two readings were virtually identical. The total number of positive and negative lymph nodes identified in each lymphadenectomy specimen was obtained from the pathology reports. When pathology slides of the lymph nodes were available, the actual number of node profiles containing tumor was verified.

The selection of the factors to be statistically analyzed was based on the investigators' clinical experience, on examination of published literature, and on preliminary reviews of the data from the present study. Sufficient clinical and histologic data were available for valid statistical analysis of the following factors: age, sex, parity, site of primary lesion, presence of satellitosis, clinical status of nodes, number of histologically positive lymph nodes, and the histologic characteristics of the primary lesion noted above. Survival was computed as the *time from date of lymphadenectomy to last follow-up or death.* Of the patients who died, all but two had clinically detectable or autopsy-confirmed melanoma as the cause of death. Since an autopsy was not performed on either of these two patients, they were treated in the statistical analysis as having died with disease.

Survival curves were calculated using the Kaplan-Meier estimate.[20] The proportional hazards model developed by Cox[11] was used to test for differences in the survival of patients within different subcategories of each factor. When only one factor is considered, this procedure is similar to the Mantel-Haenszel, or log-rank test. This procedure tests differences during the entire period of the survival curve; therefore, five-year survival rates are given for illustrative purposes only.

The Cox procedure may be used with both continuous and categorizable variables, and allows one to identify, in a stepwise manner, those factors most highly related to survival. Variables such as the number of tumor-containing nodes were analyzed first as continuous variables, and then by dividing the overall range into intervals based on experience and a consideration of the published literature. For instance, the effect of number of tumor-positive nodes on survival was analyzed using the following subcategories: 1 node positive *versus* 2-4 nodes positive *versus* 5 or more nodes positive, or 3 or fewer nodes positive *versus* 4 or more nodes positive. Subcategories were revised when preliminary analysis suggested that patients in two or more of the original subcategories could be combined on the basis of their similar survival. For each factor, the subcategory arrangement that maximally separated the subgroups and yielded the greatest statistical significance is reported. The statistical analyses using the continuous factors yielded results similar to those obtained when the factors were satisfactorily categorized.

Adequate histopathologic material was not available for some patients, particularly those seen early in the study. At each step in the (step-up) Cox analysis, data from all patients with complete information for each included factor were used. Hence, the total number of patients in the analysis decreased as the number of steps increased. To verify the results of the step-up analysis, all patients with complete data for the factors found to be prognostic when analyzed individually were selected.

A reanalysis of this limited number of patients for whom complete data were available yielded conclusions similar to those of the Cox analysis of the larger (though less complete) group of patients.

The stepwise procedure included an assessment of the statistical significance of the interaction (cross-product terms) between the factors in the Cox model. The interaction would be significant if the effect of a factor on survival were significantly different among patients with varying levels of another factor. For example, the interaction between tumor thickness and number of tumor-positive nodes would be significant if patients with four or more tumor-positive nodes had increased survival when their primary tumor was less than 1.00 mm thick, but had a decreased survival when their primary tumor was more than 4.00 mm thick. This was not true.

Characteristics of patients with and without available histopathologic material were compared to assess possible sources of bias. Differences in demographic and clinical characteristics, and in survival, were not detected between these groups.

The statistical results are summarized. A detailed description of the statistical methods and analyses will be presented elsewhere.[26]

Results

Univariate Analysis (Table I)

The Kaplan–Meier estimates of survival after lymphadenectomy for the entire group of 150 Stage II melanoma patients at one, two, five, and ten years were 73, 55, 37, and 34%, respectively (Fig. 1). When the following factors were analyzed separately, no statistically significant differences in survival among patients within the different subcategories were detected: age, sex, parity, whether or not lymph nodes were clinically palpable before lymphadenectomy, location of the primary lesion, presence of satellitosis, type of biopsy (incision/excision), histogenetic pattern, level of invasion, and frequency of mitoses in the primary tumors.

In 122 patients, the number of nodes containing tumor on histopathologic examination had been recorded in the pathology report. In the remaining 28 patients, the exact number of individual nodes containing tumor was not reported. The number of tumor-positive nodes was prognostic for survival after lymphadenectomy (Fig. 2), survival decreasing with the increasing number of tumor-containing nodes. The greatest statistical significance was observed when the 95 patients who had one to three positive nodes were compared with the 27 who had four or more positive nodes ($p = 0.026$). The measured thickness of the vertically invasive component of the primary melanomas was strongly and directly correlated with survival. The greatest statistical signif-

TABLE 1. *Results of Univariate Analysis of Clinical and Histologic Data in Stage II Melanoma Patients*

	N	5YS		N	5YS		N	5YS		N	5YS		N	5YS
Age			Sex			Parity			Node Status			Number of Positive Nodes		
≤40	42	46%	Male	90	35%	Male	90	35%	Negative	29	48%	≤3	95	45%
>40	108	34%	Female	60	41%	Female − 0	15	53%	Positive	119	36%	≥4	27	21%
						Female ≥ 1	41	38%						
p		0.20			0.13			0.17			0.20			0.026
Location Primary	N	5YS	Satellitosis	N	5YS	Biopsy Type	N	5YS	Slide Availability	N	5YS	Histogenetic Pattern	N	5YS
Extremity	63	42%	Present	14	29%	Excision	116	40%	Yes	97	39%	Sup. Spread	58	41%
Axial	76	32%	Absent	106	39%	Incision	17	24%	No	53	35%	Nodular	20	21%
p		0.43			0.53			0.13			0.78			0.35
Thickness (Breslow's)	N	5YS	Clark's Level	N	5YS	Ulceration	N	5YS	Width of Ulceration	N	5YS	Frequency of Mitoses	N	5YS
0.99mm	13	62%	II	4	50%	Yes	49	34%	None	42	49%	Many	24	35%
1.00–2.99	46	46%	III	27	46%	No	43	47%	≤6mm	30	36%	Moderate	44	42%
3.00–3.99	16	31%	IV	53	37%				>6mm	13	0%	Minimal	21	41%
4.00	12	0%	V	6	0%									
p		<0.001			0.36			0.029			0.003			0.93

Results are presented for each postulated prognostic factor tested in univariate analysis. Continuous variables were tested using a variety of cut-off points, and only the most significant result for each variable is shown. Statistical significance for each univariate comparison was derived from the entire Kaplan–Meier life table curve for each factor (see Methods). Figures for five-year survival (5YS) after lymphadenectomy were derived from the Kaplan–Meier estimates and are presented for illustrative purposes only; "N" indicates the number of patients on whom data was available.

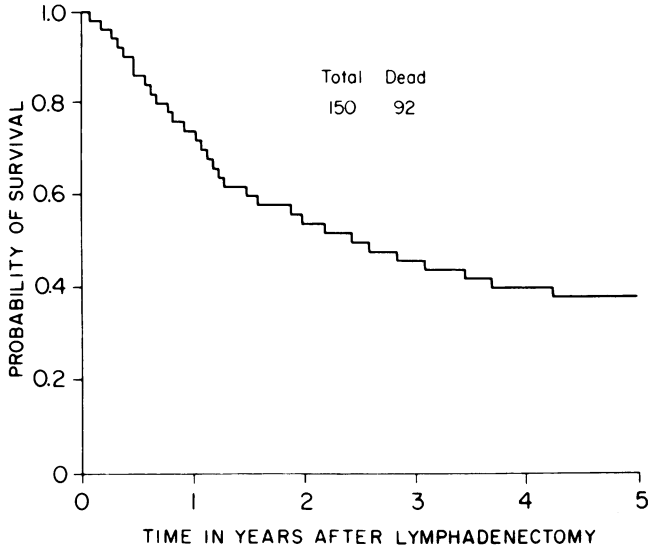

FIG. 1. Probability of survival for 150 Stage II melanoma patients.

icance was observed when groups of patients were compared with tumors ≤0.99 mm (n = 13); 1–2.99 mm (n = 46); 3.0–3.99 mm (n = 16); and ≥4.00 mm (n = 12) ($p < 0.001$) (Fig. 3).

Ulceration of the primary melanoma was an unfavorable prognostic sign (Table 1), whether assessed as the presence or absence of ulceration ($p = .029$) or the measured breadth of the ulcer: no ulceration, n = 42; ≤6 mm ulceration, n = 30; >6 mm, n = 13 ($p = 0.003$) (Fig. 4).

The univariate analysis suggested that tumor thickness, the presence and extent of ulceration of the primary melanoma, and the number of tumor-containing lymph nodes are accurate predictors of the likelihood of *survival after lymph node resection* in Stage II melanoma patients.

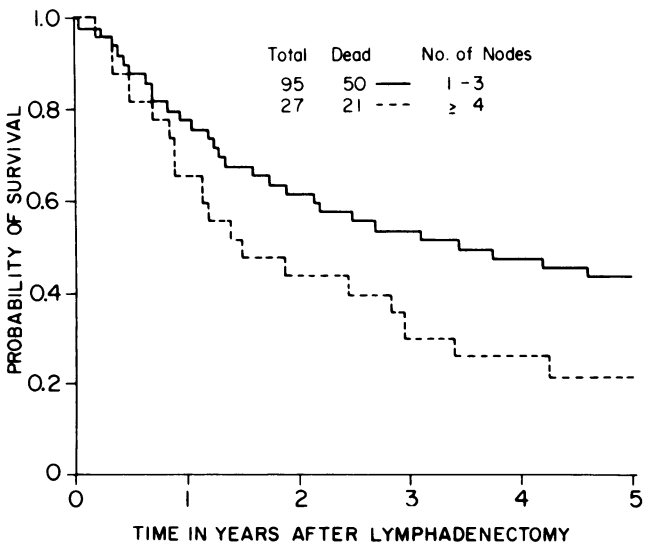

FIG. 2. Probability of survival according to number of tumor-bearing lymph nodes ($p = 0.026$).

Multivariate Analysis

In the multivariate analysis using the Cox procedure, the thickness of the primary melanoma ($p < 0.001$) and the number of melanoma-involved lymph nodes ($p = 0.04$) were the statistically significant prognostic factors. The statistical test of the interaction between thickness and number of melanoma-involved lymph nodes (the multiplicative effect of these two variables on survival) yielded a p-value of 0.10. None of the other factors analyzed in the univariate analysis achieved significance in the multivariate analysis. The presence and width of ulceration of the primary lesion, which were statistically significant factors when analyzed separately, were not significant in the multivariate analysis ($p = 0.21$ and $p = 0.19$, respectively). This was due to the strong association between the thickness categories and the width of ulceration categories (Table 1). For example, of the 13 patients with tumor thickness less than 1.00 mm, ten (83%) had no ulceration, two (17%) had a width of ulceration 6 mm or less, and none had a width of ulceration greater than 6 mm. Conversely, of the 12 patients with thickness 4.00 mm or greater, one (8%) had no ulceration, five (42%) had a width of ulceration 6 mm or less, and six (50%) had a width of ulceration greater than 6 mm. However, this strong association was due largely to our success in choosing subcategories of thickness and width of ulceration, since the correlation coefficient between these two characteristics (considered as continuous variables) was 0.35, largely due to the wide scatter of values observed.

Discussion

The cumulative five-year survival of these 150 Stage II melanoma patients was 37%, within the range of figures recorded by others (29–51%).[1,8,10,13,16,20] The therapeutic approaches recorded in these series are broadly similar to each other and to those employed in the present study. Variations in five-year results may reflect differences in surgical technique and timing, but certainly also reflect variations in referral patterns to and patient populations treated at the different centers. Although the survival figures recorded in this study and those cited previously are an improvement over older published five-year survival rates (8–25%),[12,19,25] the treatment of malignant melanoma metastatic to the regional lymph nodes remains quite unsatisfactory. This provides strong justification for the inclusion of Stage II melanoma patients in adjuvant therapy protocols.

Balch,[3] Cohen,[10] and Day et al.[14] have demonstrated

that in melanoma patients treated by wide excision of the primary tumor and lymphadenectomy, the presence or absence of histologically confirmed tumor in the excised nodes is the most important prognostic factor. In patients with no tumor in their nodes (Stage I), Cohen[10] found the thickness of the primary tumor the most significant prognostic factor, while Balch et al.[2] stressed additionally the significance of the measured width of ulceration of the primary tumor. In patients with histologically positive nodes (Stage II), Cohen,[10] Karakousis,[21] and Balch[1] found the number of tumor-containing nodes the main prognostic factor for survival. In addition, Balch[2] found that the presence and degree of ulceration of the primary tumor was negatively related to survival in Stage II patients after the role of the number of positive lymph nodes had been accounted for. The predictive significance of the number of tumor-positive nodes is confirmed by the present study. The number of positive lymph nodes is a measure of tumor burden and tumor cell number, and is an index of the success of a melanoma in producing cells capable of reaching the lymph nodes and proliferating and surviving in them. Alternatively, it may indicate that the patient's capacity to combat the tumor's ability to spread is relatively limited.

The greatest difference in survival was between patients with three or fewer tumorous nodes and those who had four or more nodes containing tumor. The survival of patients with one positive node, two to four positive nodes, and more than four positive nodes, the subdivisions suggested by Balch,[1] was compared. The statistical test of differences in survival using this categorization yielded a p-value of 0.053. However, the survival of patients in the first two categories was virtually identical (five-year survival of 45% and 43%, respectively). This difference from Balch's study may reflect differences in the amount of tumor in the individual nodes of the patients involved in the two studies and variations in significant characteristics of the primary lesions of the respective study group patients (see below). Day et al.,[14] studying a small group of patients with clinically negative but histologically positive nodes, arrived at a similar conclusion, though they chose to express nodal involvement as the percentage of tumor-containing nodes, patients with 20% or less of nodes involved having a very favorable prognosis and those with more than 20% of nodes positive having a highly unfavorable prognosis. Regardless of the final numbers chosen for subcategories, it is clear that Stage II melanoma patients entering future prospective trials *must* be stratified by number of nodes involved.

In the univariate analysis, three characteristics of the primary tumor, thickness, absence of ulceration, and micrometric measurement of ulceration, were prognostic for survival. In the multivariate analysis, only thickness was of independent prognostic importance, the presence and extent of ulceration being closely related to the measurement of thickness. Day et al.[14] also found primary tumor thickness an excellent predictor of prognosis in their recent study. Balch et al.[1] found ulceration important in univariate and multivariate analyses, while thickness was not important in either. The reasons for this discrepancy between the present results and those of Balch and his colleagues are unclear. The characteristics of the patients constituting the two study populations are certainly different. In the present series, the median thickness of primary tumors was 2.12 mm,

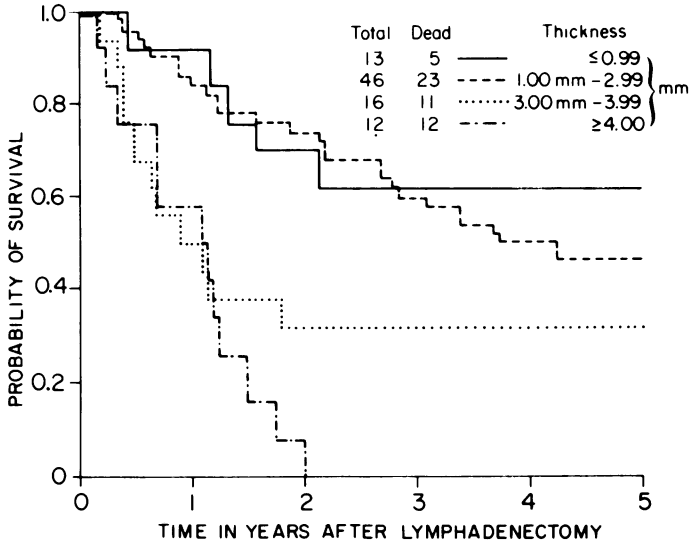

FIG. 3. Probability of survival according to thickness of the primary melanoma ($p < 0.001$).

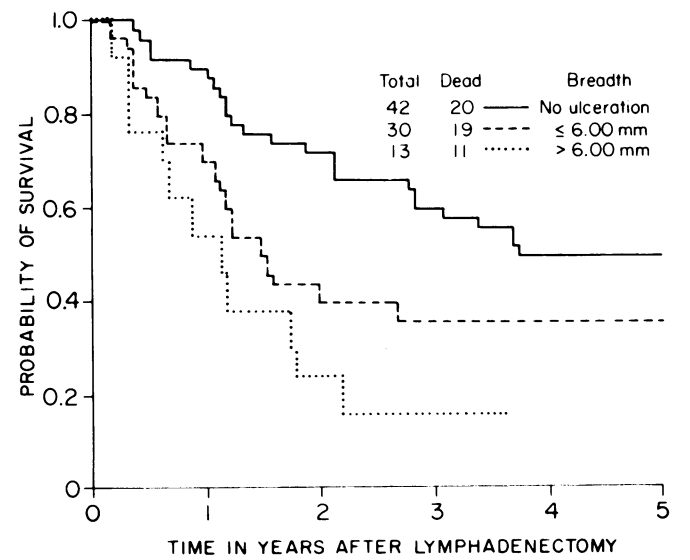

FIG. 4. Probability of survival according to presence and breadth of ulceration of the primary melanoma ($p = 0.003$).

and only 12 patients (14%) had lesions more than 4 mm thick. In Balch's series, the median thickness was 3.8 mm, and 38% of the primaries were thicker than 4 mm.

Regardless of whether the thickness of the primary tumor or the presence and extent of ulceration (these two characteristics are considered closely related) is taken as the critical feature, an important and novel concept emerges from these studies. *Characteristics of the primary tumor predict survival after therapeutic lymphadenectomy* just as much, if not more, than the time-honored parameter of the tumor burden of the nodes.

Characteristics of a primary melanoma, including thickness of the tumor and presence and extent of ulceration, correlate with the aggressiveness and duration of the tumor and the number of tumor cells present. The larger the number of tumor cells, the greater is the chance that phenotypic alterations that permit cells to spread and metastasize have occurred.

In our multivariate analysis, the statistical test of the importance of location of the primary after adjusting for primary thickness and number of tumor-positive nodes yielded a p-value that came very close to statistical significance ($p = 0.12$). In many previous studies of Stage I patients and in Cohen's[10] analysis of Stage I and II patients (1977), the site of a primary melanoma was reported to be related to survival. Balch,[1] however, did not find primary site relevant to the prognosis in his Stage II patients. This topic is clearly unsettled and worthy of future study. It would be of interest to assess the role of technical factors, such as the ease with which the different node groups may be completely excised, the assessment of tumors in anomalous "watershed" areas, and the management of multiple node groups.

Therapeutic lymphadenectomy for clinically and histologically positive nodes was carried out in 119/148 patients (80%) and elective (or prophylactic) lymphadenectomy for clinically negative histologically positive nodes in the remaining 20%. Although the group who had negative nodes on preoperative clinical assessment survived better than those with clinically positive nodes, the difference in survival was not statistically significant in either the univariate or multivariate analysis. This confirms the findings of Goldsmith,[18] Karakousis,[21] and Balch[1]; however, Cohen[10] and Das Gupta[13] have reported that node palpability prior to operation in nodes subsequently found to contain tumor on histology is an unfavorable prognostic sign. The clinical Stage I patients who were subsequently found to have tumor in their nodes were not analyzed separately but will, with patients from another source, form the subject of a future report.

This study has provided valuable descriptive information about the clinical, pathologic, and kinetic aspects of melanoma in Stage II patients, and has identified the relative importance of various prognostic factors. On the basis of the presence or absence of these factors, groups of melanoma patients can be constructed with favorable or unfavorable prognosis, as demonstrated by Roe et al.[26]

Placement in such groupings remains less than totally accurate, and, clearly, other prognostic factors, perhaps *biochemical and immunologic* in nature, must be identified before the *individual patient* can be assigned a prognosis with any degree of confidence. This is due to the large variation in survival of the Stage II melanoma patients that persisted even after the dominant prognostic factors, thickness of the primary lesion and number of melanoma-involved lymph nodes, were considered and the less important location of the primary had been accounted for.

The prognostic factors identified, number of tumor-containing nodes and thickness of the primary and possibly its location, should be employed as stratification criteria in future trials of therapy for Stage II melanoma. The current aim is to integrate these individual factors into a combined score or index, such as has been devised for primary malignant melanoma by Cochran[9] and MacKie et al.[22] Such an approach should permit the more accurate assignment of prognosis for the individual patient and reduce the number of stratification cells necessary in future randomized clinical trials.

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