A Multifactorial Analysis of Melanoma

III. Prognostic Factors in Melanoma Patients with Lymph Node Metastases (Stage II)

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Twelve prognostic features of melanoma were examined in a series of 185 patients with nodal metastases (Stage II), who underwent surgical treatment at our institution during the past 20 years. Forty-four per cent of the patients presented with synchronous nodal metastases (substage IIA), 44% of the patients had delayed nodal metastases (substage IIB), and 12% of the patients had nodal metastases from an unknown primary site (substage IIC). The patients with IIB (delayed) metastases had a better overall survival rate than patients with IIA (synchronous) metastases, when calculated from the time of diagnosis. These differences could be explained on the basis of tumor burden at the time of initial diagnosis (microscopic for IIB patients versus macroscopic for IIA patients). Once nodal metastases became evident in IIB patients, their survival rates were the same as for substage IIA patients, when calculated from the onset of nodal metastases. The survival rates for both subgroups was 28% at five years and 15% for ten years. Substage IIC patients (unknown 1° site) had better five-year survival rates (39%), but the sample size was small and the differences were not statistically significant. A multifactorial analysis was used to identify the dominant prognostic variables from among 12 clinical and pathologic parameters. Only two factors were found to independently influence survival rates: 1) the number of metastatic nodes ($p = 0.005$), and the presence or absence of ulceration ($p = 0.0019$). Additional factors considered that had either indirect or no influence on survival rates ($p > 0.10$) were: anatomic location, age, sex, remission duration, substage of disease, tumor thickness, level of invasion, pigmentation, and lymphocyte infiltration. All combinations of nodal metastases were analyzed from survival differences. The combination that showed the greatest differences was one versus two to four versus more than four nodes. Their five-year survival rates were 58%, 27% and 10%, respectively ($p < 0.001$). Ulceration of the primary cutaneous melanoma was associated with a <15% five-year survival rate, while nonulcerative melanomas had a 30% five-year survival rate ($p < 0.001$). The combination of ulceration and multiple metastatic nodes had a profound adverse effect on survival rates. While tumor thickness was the most important factor in predicting the risk of nodal metastases in Stage I patients ($p < 10^{-8}$), it had no predictive value on the patient's clinical course once nodal metastases had occurred ($p = 0.507$). The number of metastatic nodes and the presence of ulceration are important factors to account for when comparing surgical results, and when analyzing the efficacy of adjunctive systemic treatments.

THE MAJORITY OF MELANOMA patients with detectable nodal metastases (Stage II) have a high risk of microscopic metastases at distant sites, such as lung, liver, or bone. For most of these patients, the presence of distant microscopic metastases will eventually determine their fate. Nevertheless, surgical excision of metastases in the involved regional lymph node basin is important since: 1) some patients are cured with a regional operation, and 2) surgery is the most effective treatment for local control of the nodal metastases.

A prognostic factors analysis of melanoma provides useful information for evaluating results of clinical research trials involving adjunctive systemic therapy, such as chemotherapy or immunotherapy, and for making certain surgical decisions. When evaluating these treatments, it is important to identify those prognostic factors that can accurately categorize patients into different risk groups for distant metastatic disease. Otherwise, differences (or lack of differences) between adjunctive treatment regimens being compared may not be due to the treatments themselves, but may only reflect imbalances of prognostic factors. Surgical treat-

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TABLE 1. *Data Base Comparing Substages of Melanoma*

	Stage I	Stage II			
	No Evidence of Metastases*	Simultaneous Nodal Metastases (Stage IIA)	Delayed Nodal Metastases (Stage IIB)	Nodal Metastases From Unknown Primary Site (Stage IIC)	P Value†
Number of patients	249	82	82	21	—
Survival (3 years)	83%	37%	60%	50%	0.001
Primary lesion site					
lower extremity	24%	26%	21%	—	0.03
upper extremity	16%	15%	13%	—	
head and neck	34%	16%	28%	—	
trunk	24%	43%	34%	—	
other	2%	1%	7%	—	
Age (Median)	48	51	50	42	NS
Sex					
male	44%	66%	54%	71%	0.002
female	56%	34%	46%	29%	
Number of metastatic nodes					
1	—	34%	36%	53%	NS
2–4	—	49%	34%	26%	
>4	—	17%	30%	21%	
Ulceration					
yes	42%	68%	38%	—	0.0008
no	58%	32%	62%	—	
Thickness median (mm)	1.5 mm	3.8 mm	3.2 mm		
<1.5 mm	50%	12%	21%	—	0.0001
1.5–4.0 mm	36%	42%	48%	—	
>4.0 mm	14%	46%	31%	—	
Levels of invasion					
II/III	57%	20%	37%	—	0.0002
IV/V	43%	80%	63%	—	
Growth patterns					
nodular	60%	62%	63%	—	NS
superficial spreading	24%	16%	28%	—	
lentigo maleana melanoma	5%	0%	2%	—	
polypoid	11%	22%	7%	—	
Lymphocyte infiltration					
mild	27%	62%	46%	—	0.0001
moderate	51%	32%	37%	—	
heavy	22%	6%	17%	—	
Pigmentation					
yes	86%	74%	84%	—	NS
no	14%	26%	16%	—	

* Patients who had no evidence of metastases 4 years or longer after initial treatment.

† p value of correlation between the stages of disease and each prognostic factor, p values > 0.10 are defined as not statistically significant (NS).

ment decisions involve identification of patients with suspected nodal metastases who should be treated as early as possible in the natural history of their disease. Knowledge of prognostic factors can be useful for selecting the subgroup of patients with a relatively high risk for microscopic metastases in regional nodes, but who still have a relatively low risk of micrometastases at distant sites. Such patients might be candidates for immediate (or prophylactic) lymph node dissection. The rationale and surgical results of elective lymphadenectomy in our patient series have previously been published.[2,4,5]

The purpose of this study involving Stage II melanoma patients was: 1) to examine the natural history of surgically-treated metastatic melanomas in regional nodes, 2) to analyze our surgical results and some details of surgical management in these patients and 3) to compare the relative value of prognostic factors that can define different risk categories of patients, and predict their clinical course. A multifactorial analysis is the best approach in this type of comparative study. This method examines all known prognostic factors for intercorrelations, and then compares the relative strengths of each prognostic factor. The dominant prognostic variables are identified that independently correlate with survival, while accounting for the contribution of all the other factors. We have previously employed a multifactorial analysis to compare different clinical and histopathologic features of melanoma for our entire series of patients,[3] and for

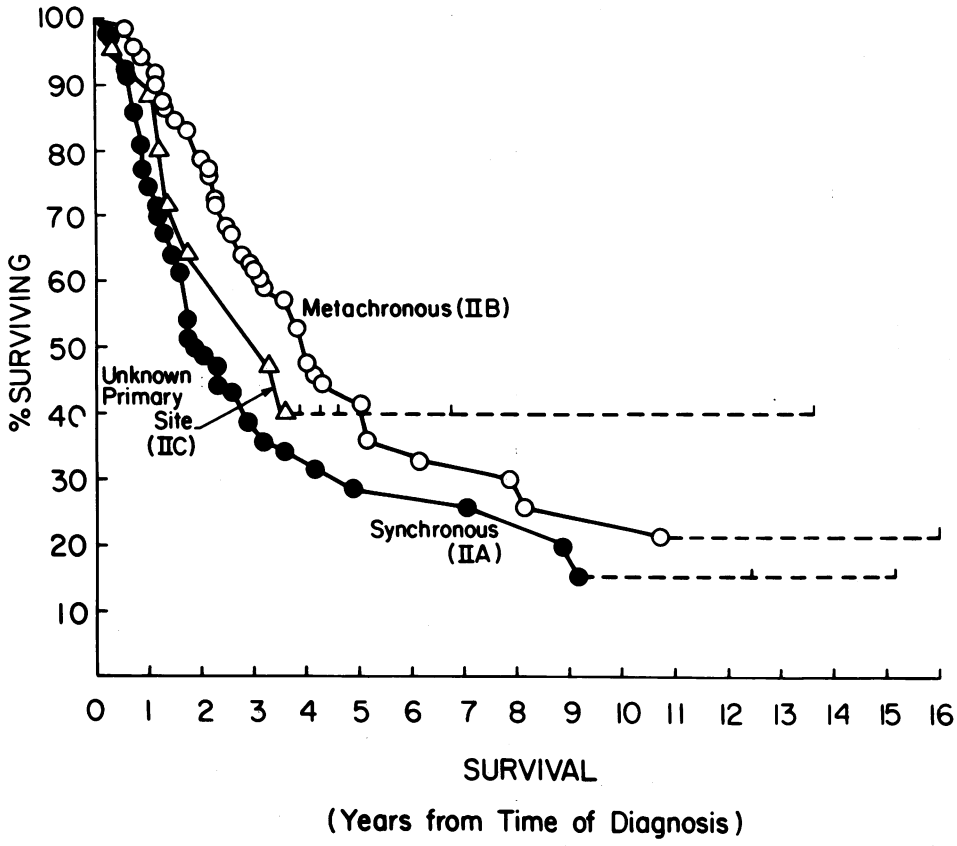

FIG. 1. Survival curves for substages of nodal metastases calculated from the time of diagnosis. Three-year survival rates for patients presenting with delayed nodal metastases (substage IIB) was 60% versus 37% for patients with nodal metastases detected synchronously with the primary melanoma (substage IIA) ($p < 0.001$). There was no difference between these survival curves when they were calculated from the onset of nodal metastases; the survival rates for substage IIB patients were virtually the same as that shown in the figure for substage IIA patients.

those patients with localized (Stage I) melanoma.[5] In this analysis, we examined 12 prognostic features of melanoma in a series of 185 patients with nodal metastases who underwent surgical treatment at our institution during the past 20 years.

Materials and Methods

Patient Population

The University of Alabama Melanoma Registry began in 1975 as a prospective–retrospective data base of all melanoma patients treated at the University of Alabama since 1960. The Registry now lists 650 melanoma patients, with clinical and pathologic data recorded in a computerized format. This represents 99% of all patients treated with melanoma at this institution during the past 20 years. Follow-up information is available for over 95%. Patients with nodal metastases represent 28% of this total group. Radical lymphadenectomy was performed in all patients. The surgical procedures were performed by two of the authors for 76% of these patients. Thirty-four of these patients have received immunotherapy during the past three years, but this additional treatment modality had no influence on the survival curves or prognostic factors analysis reported in this study.

Pathologic Definitions

The original pathologic slides of the primary cutaneous melanoma were available for 65% of the Stage II patients. The biopsy slides were examined by one pathologist who did not have knowledge of the clinical course in any of these patients. Another 12% of the patients had an unknown primary melanoma, while in 23% of patients the original slides could not be obtained. A description of the pathologic staging method used in this study, including the level of invasion, tumor thickness, degree of lymphocyte infiltration, pigmentation, ulceration and regression has previously been published.[3] Pathologic examination of regional lymph nodes was performed using routine techniques by the pathology staff. One to two sections of each node were examined. Clearing techniques were not used in dissecting out the lymph nodes.

Statistical Methods

A description of the University of Alabama Melanoma Registry and the statistical methods used in this study have been published.[3,5] Survival curves were calculated based on the method of Kaplan and Meier. A generalized Wilcoxon test was used to determine if significant differences existed between curves. Chi-

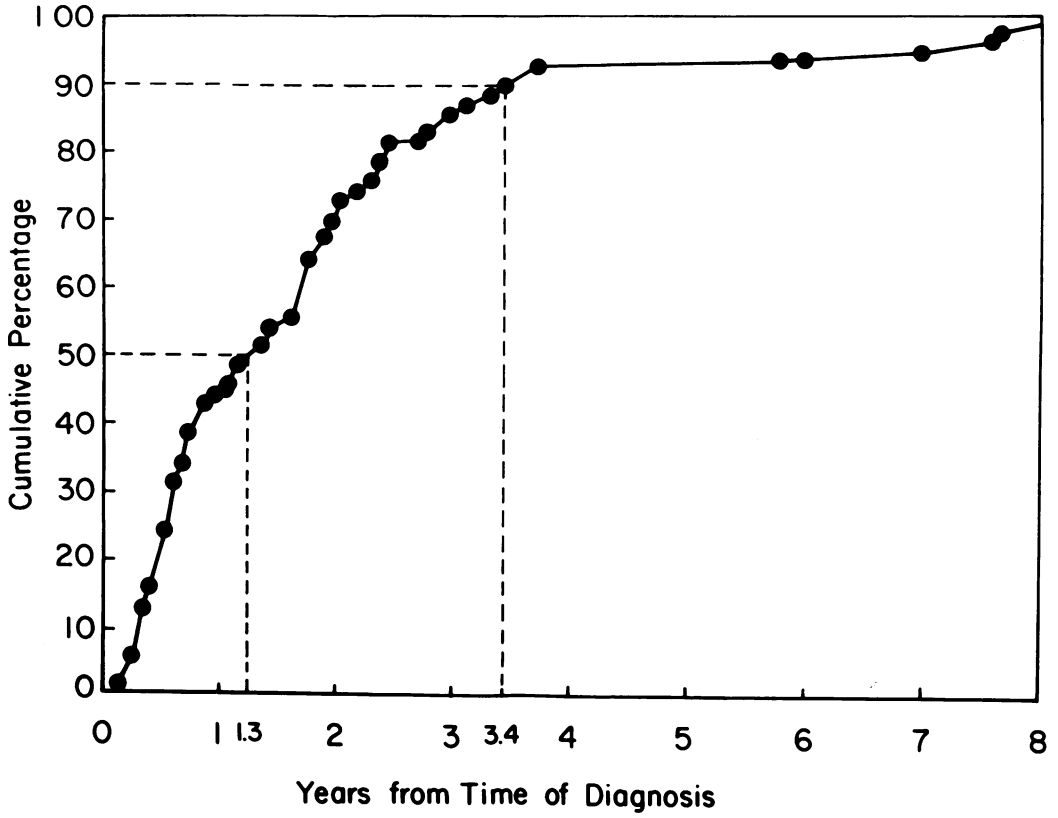

FIG. 2. Cumulative incidence of nodal metastases, in substage IIB patients, calculated from the time of diagnosis. Fifty per cent of the Stage IIB patients developed nodal metastases within 1.3 years after initial diagnosis, while 90% did so within 3.4 years.

square tests were employed in statistical assessments, where appropriate. In addition, the multiple regression procedure proposed by Cox was used in a multifactorial (multivariate) analysis of prognostic factors.[9]

Actuarial survival curves were calculated from patients who died with known melanoma; those who died without evidence of disease were computed as alive without disease for the time interval from treatment to death. In all of the calculations for prognostic factors, we have computed the survival rates from the time of initial diagnosis and from the time of nodal recurrences. In this report, survival curves are drawn as solid lines to the point of longest survival prior to death from disease; the continued broken lines indicate the survival duration of patients remaining alive.

Results

The data base for 185 patients with nodal metastases was separated into clinical and pathologic factors for each of the three substages of disease (Table 1). The results were compared with a cohort of 249 Stage I patients, who had no clinical evidence of metastases, with a minimum follow-up period of four years or longer after the initial diagnosis.

Clinical Factors

Substage of disease. Eighty-two patients (44%) presented with a primary cutaneous melanoma and synchronous nodal metastases (designated substage IIA), while the same number of patients had delayed (metachronous) metastases after previous treatment of their primary melanomas (designated substage IIB). Twenty-one patients (12%) had nodal metastases from a melanoma arising from an unknown primary site (substage IIC). When the data were analyzed from the time of initial diagnosis, patients with metachronous nodal metastases had better survival rates than those with synchronous metastases (Fig. 1). For example, the three-year survival rate for substage IIB melanoma was 60% compared with 37% for substage IIA melanoma ($p = 0.001$). Half of the patients with substage IIB melanoma developed clinically detectable nodal metastases within 1.3 years, while 90% did so within 3.4 years (Fig. 2). When the same survival data were calculated from the onset of detectable nodal metastases, there were no differences in survival rates of patients with either substage IIA or IIB (data not shown). The five-year survival rates were 28%, while ten-year survival rates were only 15%. Melanoma from an unknown primary site (substage IIC) had a slightly better associated survival rate, with 39% of

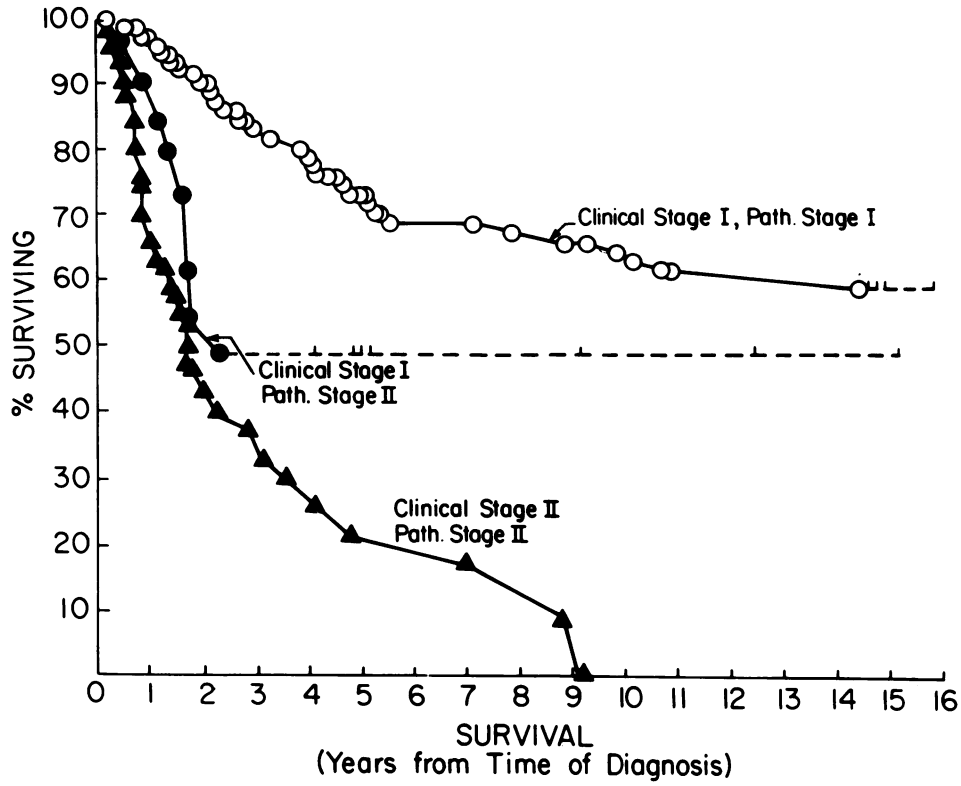

FIG. 3. Survival curves comparing clinical versus pathologic staging. Pathologic Stage I melanoma patients had a 73% five-year survival rate, compared with those patients with clinical and pathologic Stage II melanoma, who had a 24% five-year survival rate ($p < 0.001$). Patients with clinically-occult metastatic nodes (clinical Stage I, pathologic Stage II) had a five-year survival rate of less than 48%. The difference between survival curves comparing occult versus palpable nodal metastases had a p value of borderline significance ($p = 0.08$).

patients alive at five years. The differences were not statistically significant from those of IIA and IIB patients.

There were no available data relating the measured size of nodal metastases with survival rates. This information was, therefore, considered from an indirect perspective, by comparing clinical versus pathologic stage of disease, and assuming that nodal metastases found in the surgical specimen, but not appreciated clinically, were less than 1 cm in size. These patients, with clinically occult nodal metastases (clinical Stage I, pathologic Stage II) had less than a 48% five-year survival, compared with a 24% survival rate for those patients with clinically detectable nodal metastases (clinical Stage II, pathologic Stage II) (Fig. 3). The p value of differences between the entire survival curves had only borderline significance ($p = 0.08$), because the curves paralleled each other quite closely during the first two years. By comparison, patients with pathologic Stage I (localized) melanoma had a better survival rate than any subgroup of patients with nodal metastases ($p < 0.001$).

Remission duration. The remission duration between the initial diagnosis and the onset of nodal metastases was examined in the cohort of 82 substage IIB patients. Survival rates were the same for patients who developed clinically detectable nodal metastases between one to 12 months, and between 13–24 months after the initial diagnosis (Fig. 4). There was a trend for patients who had a remission duration exceeding two years to have better survival rates, but the differences were not statistically significant from any other subgroup.

Anatomic location. Primary melanoma with nodal metastases occurred in anatomic locations that were distributed throughout the body, with 54% of the melanomas in an axial location (trunk and head and neck), 33% of the melanomas located on the extremities, and 12% of the melanomas from an unknown primary site. Trunk melanomas constituted the largest group, (35% of the entire series and 43% for substage IIA melanomas). There were no statistically significant differences in survival rates for melanomas among these various anatomic locations, even when the data was cross-analyzed by substages of disease, sex and the number of metastatic nodes.

Age. Older patients with melanomas had a tendency to have a worse prognosis than younger patients. For example, only 28% of patients who were older than 60 years at the time of initial diagnosis were alive at three years, compared with 40% for patients who developed melanoma when they were less than 60 years of age. These differences were not statistically significant. The median age of the entire Stage II population was 50 years.

Sex. The majority (62%) of patients with Stage II

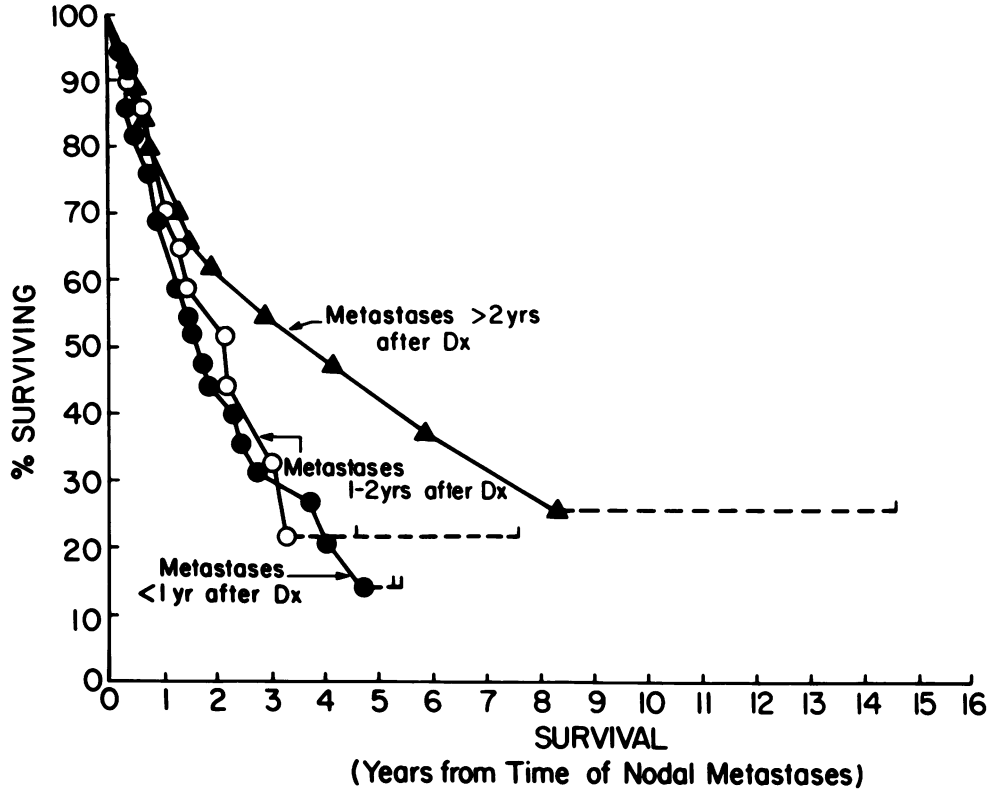

FIG. 4. Survival curves comparing different remission durations in substage IIB patients. There was no difference in survival rates for patients who had nodal metastases that occurred within one year after the initial diagnosis, compared with patients who had nodal metastases within one to two years after the initial diagnosis. There was a trend for patients with remission durations exceeding two years to have improved survival rates, but the differences were not statistically significant.

melanoma were males, compared with a lower 44% male distribution among Stage I melanoma patients. There were no differences in survival rates among male and female Stage II melanoma patients, even when the data was cross-analyzed by other categories.

Pathologic Factors

Number of metastatic nodes. There was a direct correlation between the number of metastatic nodes and patients survival rates. Patients with one metas-

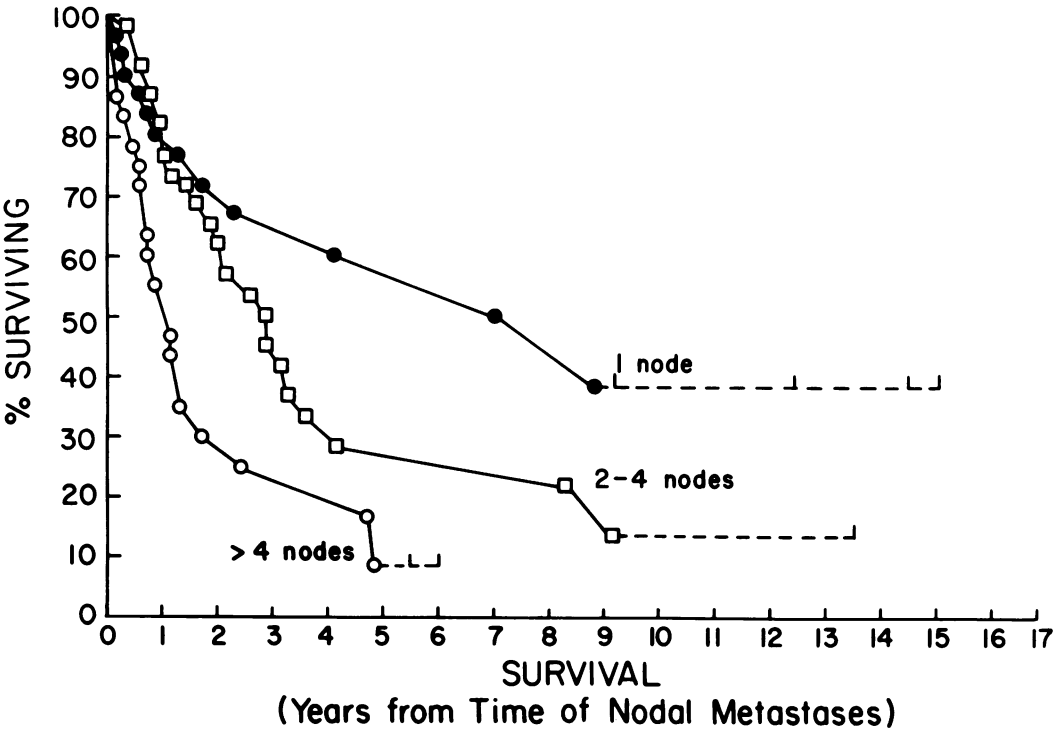

FIG. 5. Survival curves comparing the number of metastatic lymph nodes. The combination of nodal metastases that showed the greatest differences in survival rates was one versus two to four versus more than four nodes ($p < 0.001$). These differences were significant whether the survival curves were calculated from the time of initial diagnosis or from the onset of nodal metastases.

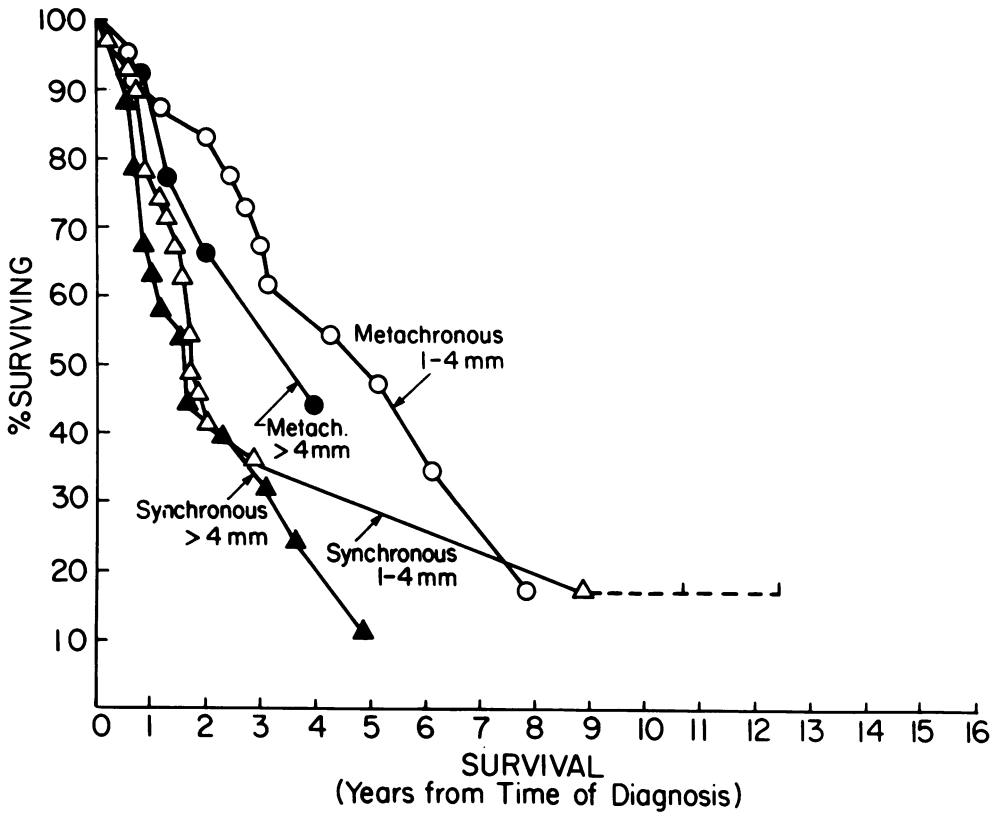

FIG. 6. Survival curves comparing tumor thickness and substage of disease. When matched for thickness, substage IIB patients with delayed nodal metastases had better survival rates, compared with patients with synchronous nodal metastases, when calculated from the time of initial diagnosis ($p < 0.05$). However, there was no difference between these survival curves when they were calculated from the onset of nodal metastases; the survival rates for substage IIB patients were virtually the same as that shown in this figure for substage IIA patients.

tatic node had a better survival rate than patients with two nodes, or any multiples of metastatic nodes. All combinations of nodal metastases were analyzed for survival differences. The combination that showed the greatest differences was one versus two to four versus more than four nodes (Fig. 5). Thirty-seven per cent (37%) of the patients had one positive node, 41% of the patients had two to four positive nodes and 22% of the patients had five or more metastatic nodes. Their three-year survival rates were 66%, 38%, and 20%, respectively ($p < 0.001$). Ten-year survival rates demonstrated that only patients with only one

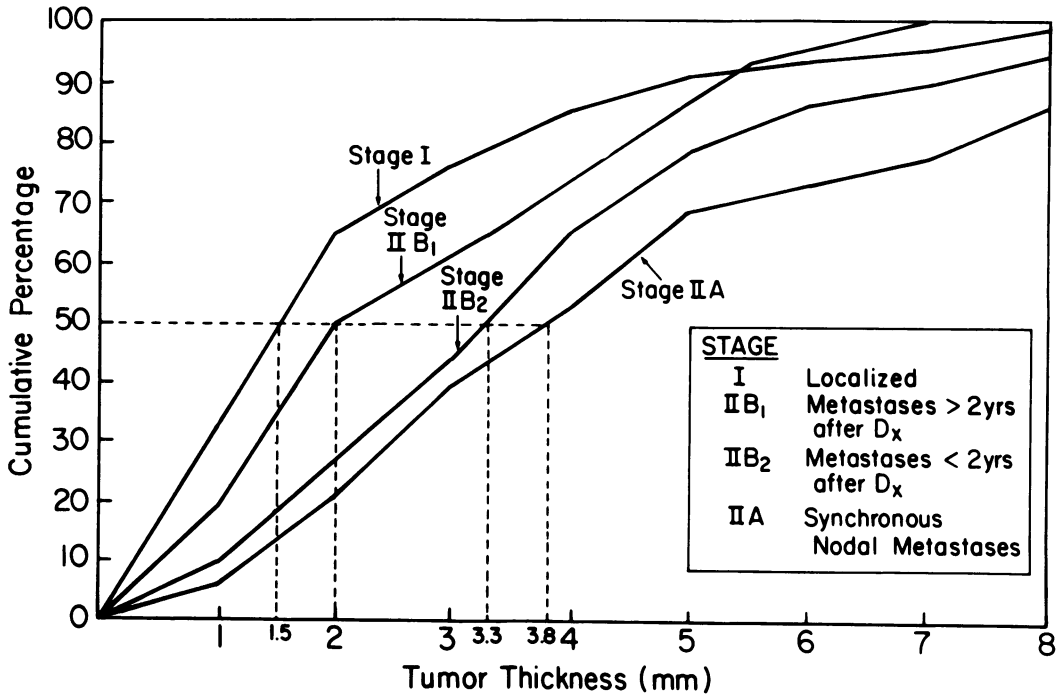

FIG. 7. Cumulative incidence of tumor thickness for each substage of melanoma. Stage II patients whose nodal metastases occurred simultaneously (IIA) or within two years after the diagnosis (IIB_1) had thicker melanomas, compared with those whose remission duration exceeded two years (IIB_2). The thinnest melanomas occurred in patients with apparently localized melanomas (Stage I).

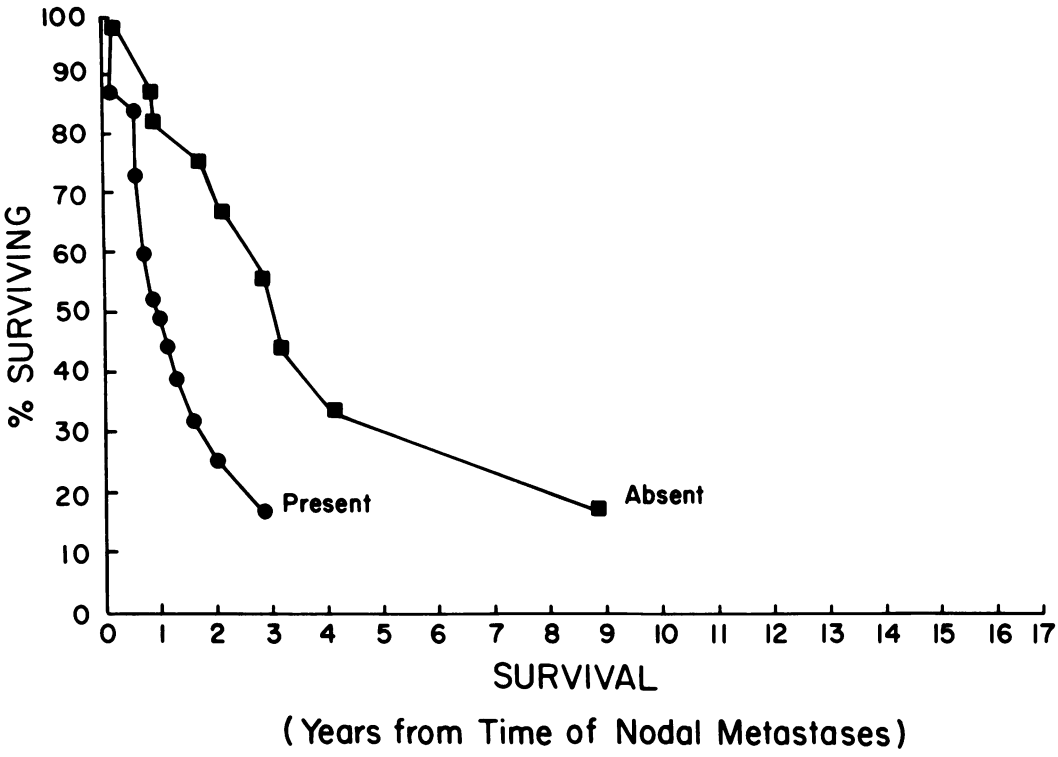

FIG. 8. Survival curves comparing the presence or absence of ulceration in Stage II melanoma patients. The difference between the two curves was highly significant, regardless of whether survival rates were calculated from the time of initial diagnosis or from the onset of nodal metastases ($p < 0.001$).

positive node had a reasonable prospect of cure (40% were alive), while only 10% or less of the patients with two or more metastatic nodes were alive at ten years.

Nodal metastases occurred most commonly in the axillae (43%), with equal distribution among cervical and inguinal areas (27% each). When survival rates for each number of metastatic nodes was further subdivided by anatomic location (extremity versus axial), there were no differences among these groups. Metastases were identified very infrequently (one to three patients each) in other nodal sites, such as in epitrochlear nodes, popliteal nodes, scapular nodes, and lower chest wall nodes.

Melanoma thickness. The median thickness for Stage II melanomas was 3.8 mm, compared with 1.5 mm for Stage I lesions ($p < 0.001$). Forty-six per cent of the patients with Stage IIA disease had thick melanomas (greater than 4 mm), while only 31% of the patients with Stage IIB disease had thick melanomas. There were five patients who developed nodal metastases with melanomas less than 0.75 mm thickness. One of these patients (with a melanoma measuring 0.71 mm) presented with clinical Stage I melanoma, and later developed nodal metastases. The other four lesions presented with Stage IIA disease and, in all cases, there were areas of significant regression in the primary lesion. Thickness, therefore, is not an accurate prognostic parameter in these regressing melanomas, a finding made previously by others.[28-30]

Melanoma thickness was used to examine whether the different substages of melanoma patients might reflect different times in the evolution of their nodal metastases. As shown in Figure 6, there was a progressive increase in the primary melanoma thickness with more advanced stages of disease. Patients without any metastases four years or longer after wide excision of their primary melanomas had the thinnest lesions (median: 1.5 mm), while those patients with occult nodal metastases that required two years or longer to reach a clinically detectable size (Stage IIB_1), had a median thickness of 2.0 mm (Fig. 6). Those patients with subclinical nodal metastases that enlarged to clinically detectable size within two years (Stage IIB_2) had a median thickness of 3.3 mm. Stage IIA patients, who presented initially with metastases sufficiently large to palpate, had the greatest vertical growth of their melanoma, with a median thickness of 3.8 mm. Thus, one primary difference between Stage IIA and Stage IIB patients is that the latter group were apparently diagnosed at an earlier stage in the natural history of their disease.

These differences among melanoma thickness categories were also reflected in survival rates, but the results depended on how the actuarial curves were calculated. Stage IIB melanoma patients had a better survival rate than substage IIA patients, when matched for thickness groups and calculated from the time of diagnosis ($p < 0.05$) (Fig. 6). Stage IIB patients with

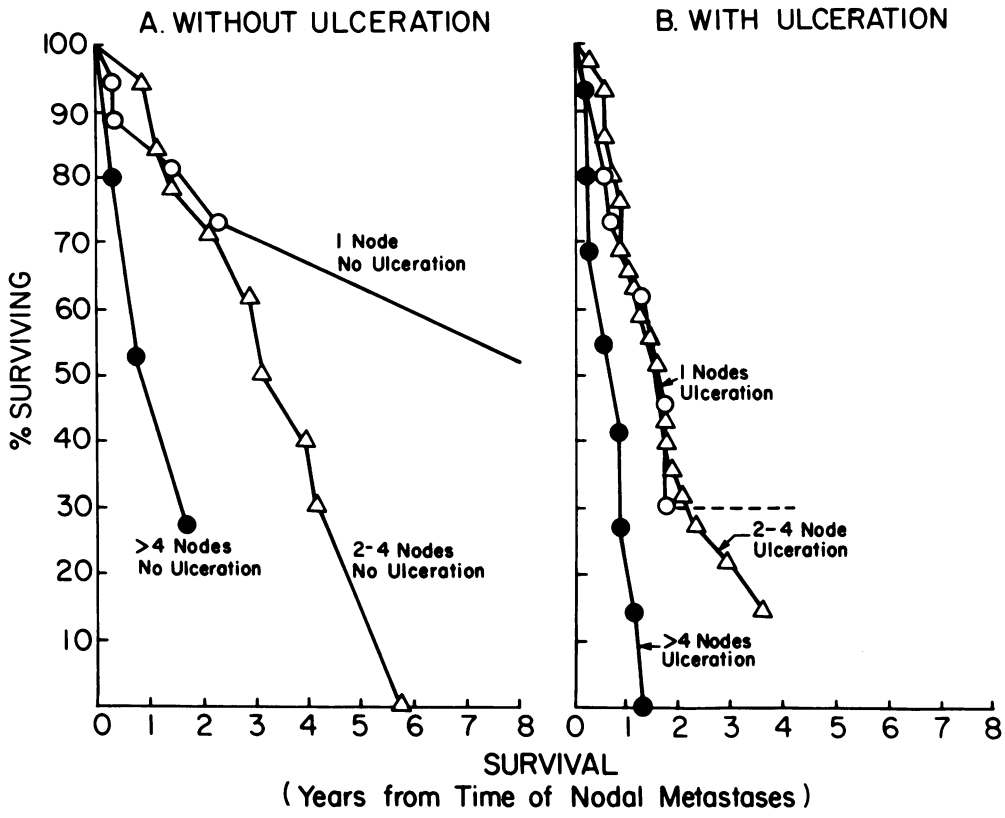

FIG. 9. Survival curves cross-analyzing the metastatic nodal status with ulceration of the primary cutaneous melanoma. The presence of ulceration had a significant adverse effect on survival curves categorized by the number of metastatic nodes.

intermediate thickness melanomas (0.75–4.0 mm) had a slightly better three-year survival rate than those with thick (≥4.0 mm) lesions (65 vs 54%). However, once nodal metastases were documented, the tumor thickness no longer predicted the clinical course of disease. Thus, the thickness of the primary melanoma had no correlation with survival rates for either Stage IIA or Stage IIB patients, when calculated from the onset of pathologically confirmed nodal metastases.

Level of invasion. Eighty per cent of the patients with Substage IIA melanoma had a level IV or level V invasion. A slightly lower distribution was seen in patients with Stage IIB melanoma, where 63% had level IV or V lesions. As with thickness, the level of invasion did not predict the subsequent clinical course of melanoma patients once they developed nodal metastases.

Ulceration. Ulceration of the epithelium overlying a cutaneous melanoma, as seen on microscopic sections, was an extremely important prognostic factor. In fact, ulceration was the only characteristic of the primary melanoma that predicted the risk of subsequent nodal metastases in Stage I patients, and continued to be an important predictive factor once nodal metastases had occurred. The three-year survival rate for Stage II patients with ulcerative melanomas was only 15%, compared with 55% for nonulcerative melanomas ($p < 0.001$) (Fig. 8). When ulceration was cross analyzed with the number of metastatic nodes, it was evident that there was some interaction between these two important prognostic factors. For each category of metastatic nodes, the presence of ulceration in the primary lesion implied a worse prognosis than if the melanoma had an intact overlying epithelium (Fig. 9). Thus, patients with one positive node and no ulceration of their primary melanoma had the most favorable prognosis of any patient group, having a 50% ten-year survival. In contrast, patients with four or more positive nodes *and* ulceration of the primary melanoma had an extremely poor prognosis, since none of the ten patients in this category survived more than 14 months (Fig. 9).

Lymphocyte infiltration. The degree of lymphocyte infiltration around the primary melanoma may be a crude index of host immune reaction to the melanoma cells. In patients with nodal metastases, only a minority of patients (38%) had a moderate to heavy lymphocyte infiltration. This contrasts with Stage I melanoma where 73% of patients had this degree of lymphocyte infiltration ($p < 0.0001$). Thus, the magnitude of lymphocyte infiltration around a cutaneous melanoma diminished as the stage of disease and the tumor thickness increased. Despite this finding, there was no difference in the survival rates of patients who had

TABLE 2. *Prognostic Factors Analysis*

Single factor analysis	
number of nodes	0.0002
ulceration	0.0006
location (extremity versus axial)	0.1213
remission duration	0.1840
age	0.2169
lymphocyte infiltration	0.3176
synch. versus metach.	0.3499
clark's level	0.4894
thickness	0.5072
pigmentation	0.5200
growth pattern	0.5298
sex	0.9719
Multifactorial analysis*	
number of nodes	0.0005
ulceration	0.0019

* All other factors had a $p > 0.10$.

minimal lymphocyte infiltration, compared with those with heavy lymphocyte infiltration.

Pigmentation. Only 21% of melanomas had no pigmentation, but this variable was not associated with different survival rates when compared with patients with heavy pigmentation.

Growth pattern. Patients with stage IIA melanomas had a high incidence (84%) of nodular growth patterns (including polypoid melanomas), while patients with Stage IIB melanomas had a nodular growth pattern in a lower percentage (70%) of patients. However, there was no difference in the survival rates, whether patients had a nodular or superficial spreading growth pattern in either substage.

Multifactorial Analysis

Each of the above 12 prognostic factors was examined for its predictive value of metastatic risk and survival rate. Table 2 presents the relative importance of each single factor, unadjusted for other factors. By single factor analysis, the only significant prognostic variables were the number of metastatic nodes ($p = 0.0002$) and the presence or absence of ulceration on the primary melanoma ($p = 0.0006$). However, there could be other intercorrelations of these variables, such as anatomic location and sex. A multifactorial analysis was, therefore, performed to examine the primary predictive factors that independently correlated with survival rates, while simultaneously accounting for the contribution of the other factors listed above. Each variable was analyzed in sequence for their additive prognostic value after the preceding factors had been accounted for. The regression model obtained through a forward selection procedure was: $\log \lambda(t)/\lambda_0(t) = 0.31315$ (number of metastatic nodes) $- 0.48912$ (ulceration), where $\lambda(t)/\lambda_0(t)$ was the relative risk. The multifactorial analysis showed that only the number of nodes ($p = 0.0005$) and ulceration ($p = 0.0019$) were the dominant variables. All other factors had a p value greater than 0.10. In this analysis, the survival rates were compared using the time of nodal recurrences as the starting point.

Discussion

Melanoma patients with nodal metastases have a high risk (85%) of harboring microscopic metastases at distant sites when metastases become clinically detectable in regional lymph nodes. Nevertheless, Stage II melanoma patients are a heterogenous group, with some patients who are cured with surgery and others who have different durations of remission and clinical course after developing metastatic disease. More than two-thirds of nodal metastases will become clinically evident within two years after the initial diagnosis, while less than 5% of patients will have relapses after five years. This observation confirms similar results at other institutions.[8,25,31]

There were different sets of prognostic factors that predicted the behavior of nodal metastases during its evolution from microscopic to macroscopic in size. In patients with clinical Stage I melanoma, the risk of microscopic metastases in regional nodes and the overall survival is best predicted by the melanoma thickness ($p < 0.00000001$) and by ulceration ($p = 0.020$), while anatomic location of the melanoma also has some predictive value in certain patient subgroups.[3,5] However, once nodal metastases were documented pathologically, only ulceration and the number of metastatic nodes predicted the patient's subsequent clinical course. For example, tumor thickness was the most important factor in predicting the risk of nodal metastases in Stage I patients, but it had no predictive value on the patient's clinical course once nodal metastases had occurred. The anatomic location of the metastasis and the patients' sex were also not predictive of survival rates after the onset of nodal metastases, although others have found these factors to be important.[8,31]

Other investigators have also found that the nodal status is an important prognostic variable in Stage II melanoma.[8,16,23] For example, a multivariate analysis of 118 patients treated at the National Cancer Institute demonstrated that the number of metastatic lymph nodes was the most important factor in pathologic Stage II melanoma, and, further, that microstaging of the primary melanoma was of prognostic importance only in patients with histologically negative lymph nodes.[8] In their series, patients with one to three metastatic nodes had a better survival than four or more positive nodes ($p < 0.01$). Five-year survival rates for patients with a single metastatic lymph node was 40–60% in three other patient series, while it was con-

siderably lower for melanoma patients with multiple nodes.[7,16,23] These results in melanoma are also similar to those obtained in patients with breast carcinoma[13] and in head and neck carcinoma,[17] where the number of metastatic nodes is an important prognostic variable. It is, therefore, important that the pathologist carefully dissect the pathologic specimen, and report both the total number of nodes removed and the number of nodes that contained metastatic disease. Three or more sections of each lymph node, especially larger ones, should be examined.[13]

Ulceration has become one of the most important prognostic factors in our series of melanoma patients.[6] The presence or absence of ulceration, as observed on microscopic slides, predicts the clinical courses of patients with both Stage I and Stage II melanoma. In fact, it was the only significant prognostic variable for both Stage I and Stage II melanoma, even when matched for all other known prognostic factors in a multifactorial analysis. Ulceration probably reflects a more aggressive and infiltrative property of melanoma than nonulcerative lesions that push the epithelium upwards during its vertical growth phase. The importance of ulceration as a prognostic factor has been confirmed in a multifactorial analysis performed by the World Health Organization Melanoma Group.[32]

It appears that the primary reason patients with delayed metastases (substage IIB) have a better overall survival rate than those with simultaneous nodal metastases (substage IIA) is that the former patient group was diagnosed at an earlier time in the evolution of their disease. In other words, the differences could be explained on the basis of tumor burden (microscopic versus macroscopic) at the time of initial diagnosis. The evidence for this concept is as follows: 1) differences in survival curves calculated from the time of diagnosis for Stage IIA and IIB melanomas was entirely due to the one and a half- to two-year delay for nodal micrometastases to enlarge sufficiently for clinical detection in Stage IIB patients; the survival curves were identical between these two substages, if they were calculated from the onset of detectable nodal metastases. 2) The prognostic factors for Stage IIA and IIB melanomas were essentially the same (ulceration and number of metastatic nodes), when the analysis was calculated from the onset of nodal metastases. 3) There was a direct correlation between the melanoma thickness and the time of metastatic detection; patients presenting with clinically detectable nodal metastases had primary melanomas that were twice as thick as patients whose micrometastases took two years or longer to reach palpable dimensions (3.8 versus 2.0 mm thickness, respectively). 4) Patients with clinically occult nodal metastases detectable in the surgical specimen had better five-year survival rate than those with clinically detectable nodal metastases, a finding previously noted in some series,[8,10,12,16,21] although not in others.[23,36]

If it is true that nodal metastases behave similarly with approximately the same tumor burden, then nodal metastases from an unknown primary melanoma site (substage IIC) should behave similarly to substage IIA melanoma from a known primary site. Although our Stage IIC patient series was small, the survival rates were virtually the same, or even slightly better, than Stage IIA patients when matched for prognostic factors. Our results, therefore, confirm those of other investigators who also found no major difference in survival rates among melanoma patients with known and unknown primary sites, and recommended comparable surgical management for both subgroups.[1,11,20]

A partial lymph node dissection or simple excision of nodal metastases is not sufficient treatment for patients with metastatic melanoma. In two-thirds or more of these patients, metastatic disease was present in other lymph nodes. This proportion of multiple nodal metastases is similar to that in other series.[16,23] Since the surgeon's ability to detect nodal metastases by clinical criteria is not optimal, a philosophy of limited excision for only clinically detectable nodes will often compromise both the palliative and curative goals of surgical treatment.

Since our surgical results for clinical Stage II melanoma have been so poor, we have adopted a more aggressive surgical approach in the management of regional lymph nodes. Selected patients with Stage I melanoma, who are at risk for microscopic nodal metastases, undergo an immediate lymph node dissection in an effort to improve their survival rates. Tumor thickness can provide a quantitative estimate of the risk of metastatic disease in both regional nodes and at distant sites in this patient group. Elective lymphadenectomy is performed for patients with intermediate thickness melanomas (1–4 mm), since these patients have a sufficiently high risk of nodal metastases to justify the operation, but a low risk of distant disease, that would otherwise negate its benefit. A radionuclide cutaneous scan can be useful for defining ambiguous lymphatic drainage in various anatomical sites, particularly those on the trunk.[2,15,27] Our results are at variance with a randomized prospective study of extremity melanoma from the World Health Organization Melanoma Group.[34,36] However, their patients, who required delayed (therapeutic) lymph node dissection, had the same poor results after surgical treatment[36] as were observed in our series of patients, and in other series.[8,10,14,16,19,21,23,35] It is possible that differences may become apparent in the WHO Melanoma Group with longer follow-up in-

formation. Other reasons for discrepancies between our results have been discussed previously.[2,18]

Since patients with Stage II melanoma have such a high risk for distant metastases, they are ideal candidates for receiving systemic adjunctive therapy, using immunotherapy and/or chemotherapy. Unfortunately, a large number of clinical trials have, so far, failed to find a regimen that has significantly improved survival rates over prolonged follow-up periods. It will be important in future adjunctive therapy trials to have properly balanced patient groups with respect to prognostic factors. In these clinical trials, the dominant prognostic variable that should be employed as primary stratification criteria are: 1) the number of metastatic nodes and 2) the presence or absence of ulceration. In addition, the remission duration for Stage IIB patients (greater versus less than two years) and the anatomic location might be considered as secondary stratification criteria. Survival curves should be calculated from the onset of documented nodal metastases, so that the different substages of nodal metastases will be more comparable in terms of tumor burden. Accounting for these various prognostic factors would then enable a fair comparison of treatment alternatives under study, and minimize the possibility that a treatment benefit for some subgroups of patients would not otherwise be obscured.

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