Improved Long-term Survival After Lymphadenectomy of Melanoma Metastatic to Regional Nodes

Analysis of Prognostic Factors in 1134 Patients from the John Wayne Cancer Clinic

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A review of 1134 patients from the John Wayne Cancer Clinic with melanoma metastatic to regional lymph nodes was carried out to evaluate the importance of various prognostic features after lymphadenectomy. Univariate analysis identified the prognostic significance of clinical stage for lesions with a depth of 0.76 to 4.0 mm ($p = 0.0018$); number of involved nodes ($p = 0.0001$); Breslow's thickness ($p = 0.0487$); gender ($p = 0.0103$); location on an extremity ($p = 0.0104$); synchronous *versus* asynchronous detection of nodal metastases ($p = 0.0107$); age as a continuous variable ($p = 0.0670$); and unknown primary site ($p = 0.088$). Multifactorial analysis showed that number of involved nodes ($p = 0.0001$), extremity location of primary ($p = 0.0059$), and Breslow thickness ($p = 0.0334$) maintained their significance, whereas gender ($p = 0.0627$) and clinical stage ($p = 0.0942$) were almost significant. The long-term survival of the entire patient population at 5, 10, and 15 years of follow-up was estimated to be 46%, 41%, and 38%. When individual characteristics found to be significant by multivariate analysis were combined into different subsets, there was considerable heterogeneity, with 5-year survival varying from 79% to 14%. To quantify this heterogeneity better, a mathematical model was developed and found to approximate closely the observed survival rates in the heterogenous subsets and in the group as a whole.

THE INCIDENCE OF cutaneous melanoma is increasing throughout the world, particularly in those locations where people with fair complexions are exposed to sunlight. This annual rate of increase, 4%, is higher than for any other malignancy. It has been estimated that by the year 2000 one in every 90 individuals in the population will develop melanoma.[1] The presence of lymph node metastases is well established as a crucial prognostic indicator in this disease. Long-term survival after lymphadenectomy of patients with lymph node metastases (American Joint Committee on Staging [AJC] stage III) is poor, with less than 15% of patients surviving 10 years or longer in most series.[1,2] The number of involved nodes, the Breslow thickness,[3] anatomic location of the primary site, clinical status of nodes, and gender are among the factors most frequently reported to be of prognostic significance in AJC stage III disease.[1,2,4,5] The observation that survival of patients with lymph node metastases treated at the John Wayne Cancer Clinic (JWCC) appears to be higher than previously reported from other series,[5] including our own early experience, led us to review our entire experience with this stage of the disease in an attempt to explain the apparent improvement in survival rates. We undertook a univariate and multivariate analysis of the prognostic factors significant in this disease and developed a prognostic model that was predictive of survival in our patients as a whole group, as well as in the heterogenous subsets.

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Material and Methods

Patient Population

The clinical records of 5111 patients treated at the John Wayne Cancer Clinic during the 18-year period between April 1971 and January 1, 1989 were reviewed and registered into the JWCC's computerized database developed at the John Wayne Cancer Clinic. The period of follow-up observation ranged from 2 to 20 years, with only 47 patients (0.92%) in the entire series being lost to follow-up.

Regional lymph node metastases were found in 1134 patients; and 584 patients (51.1%) died. Among these

complete information was available on 737 patients regarding age, gender, anatomic location, Clark's level, and Breslow thickness of the primary site, number of involved nodes, clinical stage (I or II), timing of lymphadenectomy for clinical stage II disease, whether synchronous or asynchronous, and whether or not the patient received adjuvant immunotherapy following lymphadenectomy. This group of 737 patients was used to evaluate the significance of the various prognostic factors by univariate and multivariate analysis.

Pathology

Examination of the lymph nodes was performed using routine techniques of hematoxylin and eosin staining. In approximately 90% of patients, the number of lymph nodes containing metastatic melanoma could be accurately determined. The primary lesions were examined by the pathology staff of the Department of Pathology at UCLA, and their interpretation, as presented on the pathology report, was used as the basis of this analysis. Unfortunately data were often not uniformly recorded on certain histologic variables, such as the degree of ulceration, lymphocytic infiltration, mitotic index, and Breslow thickness of the primary lesion. From 1971 to 1978, Dr. Wallace Clark was consulted regarding the interpretation of the Breslow thickness or Clark's level of the primary when questions were raised by the staff pathologist.[6] During the past 10 years, these questions were reviewed by Dr. Alistair J. Cochran, who is currently undertaking a detailed prospective review of the histologic variables of the primary melanoma, which will be the subject of a subsequent report.

Treatment

Patients with primary lesions underwent wide excision of the primary site, according to the guidelines we have previously described.[7,8] All patients with lymph node metastases were treated with regional lymphadenectomy. Our standard operative approach for radical lymphadenectomy at various sites has been previously described.[7,9,10] Because they are at high risk for the future development of metastatic disease, many of these patients participated in adjuvant immunotherapy protocols. Approximately 55% of patients received adjuvant immunotherapy consisting of either nonspecific immunotherapy with bacille Calmette-Guérin administered by the tine technique, as previously described,[11] or active specific immunotherapy with tumor cell vaccine administered by the intradermal or intralymphatic routes.[12] Because our approach to the management of primary melanoma at various anatomic sites has been previously reported,[7] it is only briefly reviewed here with regard to special sites.

Regional Lymph Node Metastases from Melanoma of an Unknown Primary Site

A special group of patients present with regional lymph node metastasis, but without a determined site of the primary melanoma. The incidence of these patients is approximately 14% (155/1134) of all patients with lymph node metastases seen in the JWCC. Although logic suggests that these patients might fare worse than those with a known primary, a review of our experience has found their survival rate to be equal or superior to that of patients with a known primary and, in this analysis, equal to those with thin primary lesions on the extremity ($p = 0.08$). Because prognosis was nearly the same for both groups of patients, we advocate the same aggressive regional lymphadenectomy for patients with unknown primary melanoma as for those with a known primary.[13]

Melanomas Arising from the Axial Location on the Trunk or Head and Neck Primary Sites

Melanomas arising on the axial skin of the trunk, particularly those near the midline or belt line, or those near the neck, may drain to one or more lymphatic areas. Sappey[14] defined a line that is 2 cm wide and encircles the trunk at the level above and below the umbilicus. Lesions above this line generally drain to the axillary nodes, and those below the line drain to the inguinal nodes. Certain of the midline lesions, particularly those of the umbilical area or midline of the back, can drain to all four areas, however. This problem of ambiguous lymphatic drainage is one argument advanced against elective lymph node dissection (ELND) for truncal melanomas. We introduced cutaneous lymphascintigraphy in 1977 to solve this problem.[15–17] Although we initially used colloid gold, we now use a technetium (^{99}Tc)-labeled dextran lymphatic scan, during which ^{99}Tc is injected into the primary melanoma site to determine into which lymph node basins the primary melanoma might drain.[18] The procedure does not indicate nodal metastasis, but does accurately demonstrate the route of lymphatic drainage of the primary site. This technique is used to select which regional lymph nodes to remove by lymphadenectomy.

Statistical Methods

Estimated survival rates were obtained by the nonparametric Kaplan-Meier method.[19] The log-rank test was used to determine differences in survival of patients from subgroups defined by different levels of risk factors. This method of univariate analysis is useful when all variables are categorized into subgroups that are maximally separated in terms of survival rates. For example if the survival rate of patients with truncal lesions is not statistically different from that of patients with head and neck lesions, but is statistically different from that of patients with ex-

tremity lesions, the first two groups are combined and compared with the third. This technique was used in part to define categories for the risk factors tumor depth, number of nodes, and tumor location. A more general rank test than the log-rank test was used to test for multivariate association of the risk factors. A discussion of these tests can be found in Kalbfleisch and Prentice.[20] The multivariate results were confirmed using the Cox proportional hazards regression model.[21] The statistical package of SAS procedures LIFETEST[22] and PHGLM[23] were used in the univariate and multivariate analyses. Survival time was defined as the time a patient remained alive after the documented date of nodal metastatic disease at lymphadenectomy.

Results

Long-Term Survival

Table 1 shows long-term survival rates after lymphadenectomy of patients with lymph node metastases and indicates that survival at 5, 10, and 15 years was 46%, 41%, and 38%, respectively. Note that the number of patients still available for observation beyond 10 years was 197, whereas it was 87 for more than 15 years. The rate of deaths per unit of time changes dramatically after 5 years to 1% per year between years 5 and 10, and then to only 0.6% per year thereafter.

Univariate Analysis of Prognostic Factors

Table 2 lists the factors analyzed by univariate analysis. The univariate analysis shows the following factors to be of prognostic value: (1) numbers of involved nodes categorized as 1 *versus* 2 to 4 *versus* 5+ nodes (p = 0.0001); (2) extremity location of primary (p = 0104); (3) thickness of the primary lesion categorized as 0.1 to 1.49 *versus* 1.5 to 3.99 *versus* 4.0 mm (p = 0.0478); (4) gender (p = 0.0130); (5) synchronous rather than asynchronous metastases (p = 0.0107); (6) age as a continuous variable (p = 0.067); (7) clinical stage at the time of lymphadenectomy (I *vs.* II) was of prognostic significance for lesions of Breslow thickness from 0.76 to 4.0 mm (p = 0.0016) (Fig. 1), but not for those greater than 4.0 mm (p = 0.2960); and (8) unknown primary site (p = 0.0876).

TABLE 1. *Long-Term Survival of 1134 Patients with Melanoma Metastases to the Lymph Nodes Treated at the John Wayne Cancer Clinic*

Time (yr)	Survival (%)	SD	No. Dead*	No. Observed†
1	84	1.1	175	902
2	66	1.5	362	647
3	55	1.6	461	496
5	46	1.6	537	357
10	41	1.7	573	197
15	38	1.8	582	87

* Cumulative number of deaths up to the time point.
† Number of patients still under observation beyond the time point.

TABLE 2. *Analysis of Prognostic Factors by Univariate and Multivariate Methods*

Factor	p	
	Univariate	Multivariate*
No. of nodes	0.0001	0.0001
Breslow thickness	0.0487	0.0334
Sex	0.0103	0.0627
Age	0.0670	
Location of primary lesion		
Extremity	0.0104	0.0059
Unknown	0.0876	
Head and neck	0.1845	
Trunk	0.1168	
Clinical stage I *vs.* stage II		
0.76–4.00 mm	0.0016	0.0942
≥4.00 mm	0.2960	
Synchronous *vs.* metachronous	0.0170	
Clarks's level	0.3685	
Adjuvant immunotherapy	0.4118	

* Data shown only for factors with p < 0.10 by multivariate analysis.

Prognostic Factors Significant by Multivariate Analysis

The eight factors found to be most significant by univariate analysis were examined by multivariate analysis because there could be other interrelationships between these variables. For example there is a well-known relationship between the anatomic location of the primary site and gender; locations on the extremity are more frequent in women than in men. Therefore a multifactorial analysis was performed to examine primary predictive factors that independently correlated with survival rates, simultaneously accounting for the contribution made by the factors, which was found to be significant by univariate analysis. Each variable was analyzed in sequence for its

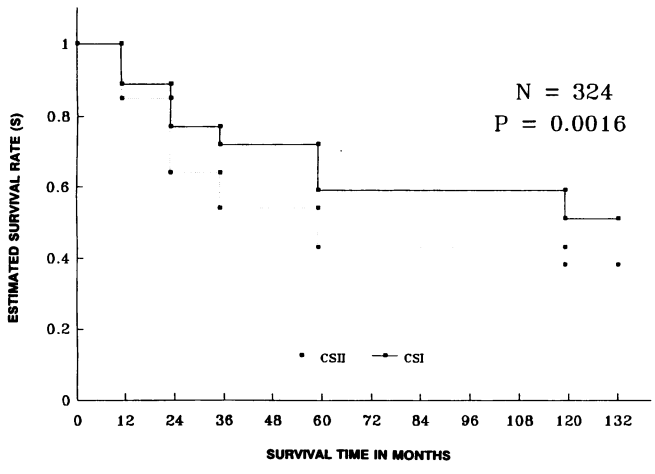

FIG. 1. Long-term survival rates of patients with lymph node metastases undergoing lymphadenectomy for clinical Stage I *versus* II disease (primary melanoma depth 0.76 to 4.0 mm).

additive prognostic value after the previously added factors had been taken into account. A general multivariate rank test was used[20] as well as the Cox proportional hazards regression model. Both methods use a forward variable selection procedure, and they provided the same results. This multifactorial analysis, which is summarized in Table 2, showed that only the number of involved nodes ($p = 0.001$), the location on an extremity ($p = 0.0059$), the depth of the primary ($p = 0.0334$), the patient's sex ($p = 0.0627$), and clinical stage ($p = 0.0942$) were dominant variables. All other factors had a p value greater than 0.10.

Development of Mathematical Prognostic Model

We next attempted to determine the importance of each of these variables in overall survival for the group. In so doing it became evident that there were some subsets of patients with regional nodal metastases who had different degrees of risk of dying from their disease. Figure 2 gives a summary of the 5-year survival rates categorized by gender, primary site, number of nodes, and thickness. Taking the standard errors into account, the 5-year rates for nonextremity lesions do not vary significantly for men and women, whereas Breslow thickness and the number of involved nodes are highly significant prognostic factors for these sites. We concluded that gender was not a prognostic factor for primary melanoma sites of the head and neck or trunk, and male and female subgroups for these sites could be combined as shown in Figure 3. For extremity melanomas and those with unknown primary site, however, the significant prognostic factors vary with gender; the number of involved nodes are important factors in women, but Breslow thickness is more significant in men. Male patients with an unknown primary site were similar to those with thin-extremity melanomas. These various prognostic factors can be combined to create three categories of melanoma patients with lymph node metastases: low risk, with expected survival of 65–75%; middle risk, with expected survival of 40% to 55%; and high risk, with expected survival of 25% to 30%.

Next we developed a mathematical model based on the prognostic value that could be placed on each of these variables and their interactions. The model is defined as a mixed exponential model. In a regular exponential model, the survival rate is defined as

$$S(t) = \exp(-\alpha t),\ t > 0,$$

where α is the hazard rate that is assumed to be constant. In a mixed exponential model, the survival rate is defined as a function of two rates and is a mixture of two different survival functions. A mixing proportion is needed so that the survival rate is always bounded between 0 and 1, in other words, $0 \leq S(t) \leq 1$. The general form of a mixed exponential model is

$$S(t) = p\exp(-\alpha_1 t) + (1-p)\exp(-\alpha_2 t),\ t > 0,$$

where α_1 and α_2 are two different rates and p is the mixing proportion. Risk factors can be included into the model by defining the rates α_1 and α_2 in terms of the risk factors. As illustrated in Figure 2, we saw many complex interactions between the risk factors that affected survival. For example there was no gender effect for patients whose primary lesion was in the extremity, although depth and the number of involved nodes were still independently important. Therefore a term was included in the model that accounts for the interaction between the lesion lo-

Extremity and unknown sites

	Males		Females	
	<1.5 mm (N)	≥1.5 mm (N)	<1.5 mm (N)	≥1.5 mm (N)
1 node	50% ± 8 (49)	45% ± 10 (29)	66% ± 7 (53)	79% ± 9 (24)
2–4 nodes	57% ± 7 (52)	48% ± 14 (20)	67% ± 8 (31)	54% ± 11 (25)
5+ nodes	46% ± 9 (32)	14% ± 13 (13)	63% ± 12 (17)	57% ± 15 (16)

Nonextremity site

	Males		Females	
	<1.5 mm (N)	≥1.5 mm (N)	<1.5 mm (N)	≥1.5 mm (N)
1 node	73% ± 8 (45)	49% ± 7 (75)	76% ± 12 (14)	45% ± 13 (23)
2–4 nodes	47% ± 10 (33)	32% ± 6 (77)	49% ± 16 (11)	35% ± 12 (22)
5+ nodes	21% ± 9 (26)	34% ± 9 (32)	44% ± 17 (10)	14% ± 13 (8)

FIG. 2. Five-year survival rate of patients with lymph node metastases according to prognostic factors.

Extremity and unknown sites

Male*

<1.5 mm	≥1.5 mm
50%	40%

Female†

1 node	2–4 nodes	5+ nodes
70%	60%	55%

Nonextremity site‡

	<1.5 mm	≥1.5 mm
1 node	70%	50%
2–4 nodes	50%	30%
5+ nodes	30%	25%

* Number of involved nodes is insignificant for males.
† Thickness is insignificant for females.
‡ Sex is an insignificant factor for nonextremity lesions.

FIG. 3. Five-year survival rate of patients with lymph node metastases according to prognostic factors.

cation and gender. For patients with nonextremity lesions, the relationships between gender, depth, and the number of nodes was more complicated because gender did not appear to be of importance for nonextremity sites. In particular we saw that depth was not a prognostic factor for females, but that the number of nodes remained important. Males with nonextremity lesions were observed to have different rates of survival for different thicknesses but the number of nodes did not decrease the survival rates as expected.

Table 3 gives the coding of all risk factors and interaction factors in the model. Three interaction variables, extremity and gender (X_7), gender and node (X_8), and gender and depth (X_9), account for the complex interactions we observed in this dataset. For example the interaction variable X_7 is 0 when the variable indicating tumor location (X_5) is 0. This means that the site of the lesion is not on an extremity and indicates that the effect of gender is 0. The 5-year survival rates of the JWCC database confirm this observation. In particular the estimated mixed exponential model is defined as:

$$\hat{S}(t) = 0.7 \exp(-\hat{\alpha}_1 t) + 0.3 \exp(-\hat{\alpha}_2 t)\ t > 0,$$

where

$$\ln(\hat{\alpha}_1) = \exp[-(3.864 - [0.511*X_3 + 0.7388*X_4]*X_8 - [0.4173*X_2]*X_9 + 0.08*X_6 + 0.59*X_7)]$$

and

$$\ln(\hat{\alpha}_2) = \exp[-(7.327 - [0.417*X_3 + 0.6732*X_4]*X_8 - [0.4321*X_2]*X_9 + 0.19*X_6 + 0.071*X_7)].$$

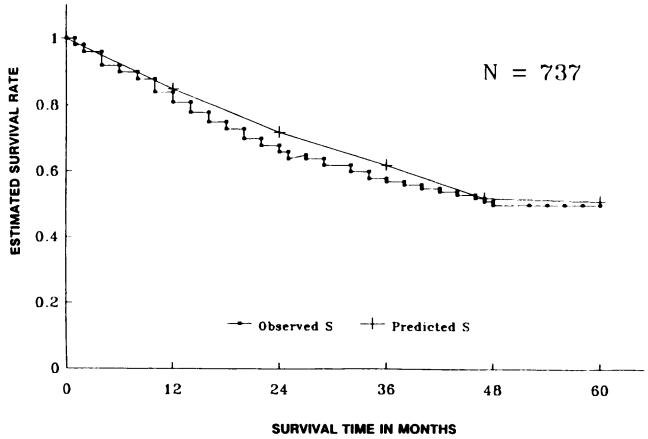

FIG. 4. Observed and predicted survival rates for all patients.

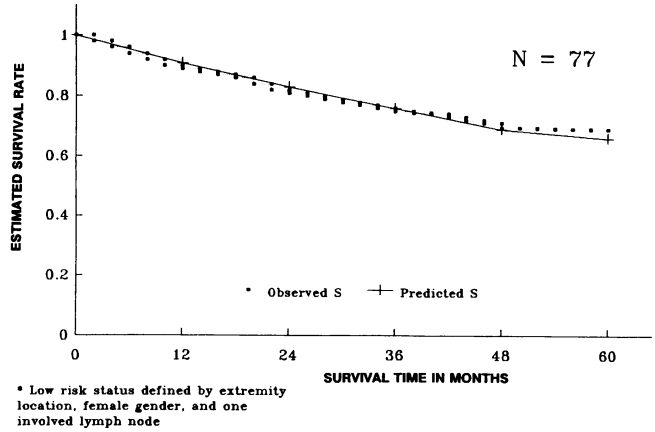

FIG. 5. Observed and predicted survival rates for low-risk group.

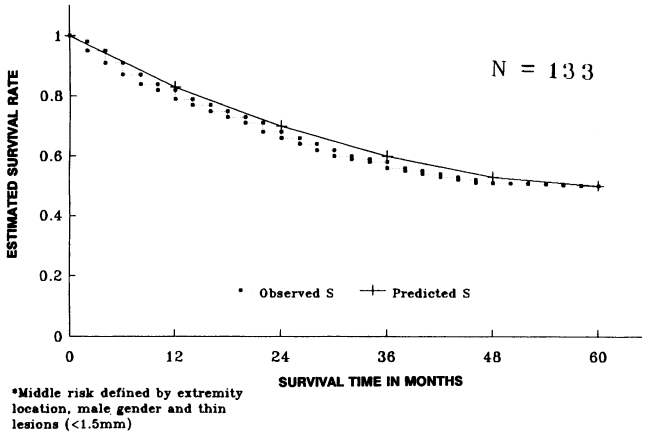

FIG. 6. Observed and predicted survival rates for middle-risk group.

Comparison of Observed Survival with That Predicted by the Mathematical Model

Figure 4 gives the overall observed survival *versus* that expected by our model. Figures 5, 6, and 7 compare the observed *versus* the expected survivals for selected subsets of patients at low, medium, and high risk. It will be noted that the mathematical model closely parallels the observed survival and does not significantly deviate from it during the first 5 years. After 5 years the observed risk can be accurately estimated by using a risk factor of 1% per year between years 5 and 10.

Discussion

In the present study, the prognosis of patients with metastases to the regional lymph nodes depended on a number of factors, the most important of which are the number of involved lymph nodes, the depth of invasion of the primary melanoma, the sex of the patient, and the site of the primary melanoma. As clearly indicated by this study, there is great heterogeneity in the prognosis of patients with lymph node metastases; some subsets may have expected survival rates of as high as 79%; whereas others may be as low as 14% (Fig. 2). Thus it is critical that these important prognostic factors be considered when giving prognostic information to the individual patient, as well as when evaluating the results of trials of adjuvant therapy.

TABLE 3. *Coding of Risk Factors for the Mathematical Model*

Factor	Defined Factor (X_i) in the Model	Coding for the Factor X_i
Sex	X_1	1 = F; −1 = M
Tumor depth	X_2	0 = <1.5 mm 1 = ≥1.5 mm
No. of involved lymph nodes	X_3	1 = 2–4 nodes 0 = other than 2–4 nodes
	X_4	1 = 5+ nodes 0 = other than 5+ nodes
Lesion location	X_5	1 = extremity 0 = nonextremity
Survival time	X_6	1 = patient still alive after 36 mo 0 = patient not observed after 36 mo
Interaction variables with lesion location		
Sex	X_7	0 = nonextremity −1 = extremity, M 1 = extremity, F
Sex and nodes	X_8	0 = extremity, M 1 = extremity, F
Sex and tumor depth	X_9	0 = extremity, F 1 = extremity, M

The present study confirms our initial impression that the overall survival results have improved to a 5-year survival rate of 46% compared with our earlier series in which only 37% of 150 patients with melanoma who were seen between 1954 and 1976 survived.[5] These patients were treated by lymphadenectomy but received neither chemotherapy nor immunotherapy. The clinical course of these patients up to the point of the development of post-lymphadenectomy metastases was representative of the "natural history" of the disease treated by surgery alone. The explanation for this improvement is not readily evident, because the distribution of patients with regard to nodal status and other features is similar.

This study confirmed the predictive significance of the number of tumor-positive nodes and thickness of the primary melanoma. The number of positive lymph nodes appears to be a measure of tumor burden and their metastatic potential and served to show that the primary melanoma could produce cells capable not only of reaching the lymph nodes but also of proliferating and surviving in them. Alternatively the number of positive nodes may indicate that the patient's capacity to combat the melanoma's ability to spread is relatively limited. More recent studies from our laboratory have indicated the immunodepression exhibited by the lymph nodes draining the primary melanoma.[22]

The greatest difference in survival observed in our early report was between patients with one tumorous node and those who had five or more positive nodes. In univariate analysis characteristics of the thickness of the primary, the absence of ulceration, and the micrometric measurement of ulceration were prognostic for survival. In the multivariate analysis, only thickness was of prognostic significance, because the presence and extent of ulceration were closely related to the measurement of thickness. It is of interest to note that these characteristics of the primary tumor also could predict survival in a manner similar to the time-honored parameter of tumor burden in the nodes. In fact thickness appears to be more important than the number of nodes for extremity lesions in men. It is likely that these characteristics correlated with the aggressiveness and duration of the primary melanoma and with the number of tumor cells present. The larger the number of tumor cells, the greater the chance of phenotypic alterations that permit cells to spread and metas-

tasize. When analyzed separately in the univariate test, other factors including age, gender, 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 tumor, did not disclose any statistically significant differences in survival among patients within the different subcategories. By multivariate analysis, however, the importance of the location of the primary after adjusting for primary thickness and the number of tumor-positive nodes yielded a p value that was highly significant. The volume of metastic melanoma in each involved node that had previously been found to be highly significant could not be accurately evaluated in this retrospective study,[24] except indirectly by the number of involved nodes and their clinical status (I *vs.* II).

The large number of patients in this series, which we believe to be the most yet reported, allowed us to evaluate a greater number of variables by multivariate analysis, while maintaining adequate sample sizes to ensure statistical power. We observed remarkable heterogeneity, however, between various subsets of patients based on the prognostic factors found to be significant by multivariate analysis. This can best be observed in Figure 3. The tremendous variation between a 70% survival in the low-risk group *versus* only 25% to 30% survival in the high-risk group indicates the importance of accurately quantifying these factors when comparing series of patients with lymph node metastases. This is especially important when evaluating the results of adjuvant therapy where variations in the natural history of the disease managed by surgery alone are so heterogeneous that it probably exceeds the expected effect of most adjuvant therapies.

Therapeutic Lymphadenectomy

There is general agreement that regional lymphadenectomy is indicated for the patient who has clinically suspicious or pathologically proved metastasis to regional lymph nodes. Contrary to the pessimism in the early literature, we found that 38% of such patients will survive 10 years, and the patients with thin melanoma and only one clinically positive lymph node may have a 5-year survival as high as 79%. Therefore patients with clinically involved regional nodes should not be considered as being incurable due to occult distant metastatic disease, because a significant proportion can benefit from surgical resection.

Results of Therapeutic Versus *Elective Lymphadenectomy: Clinical Status of Regional Nodes—Clinical Stage I* Versus *II*

Our results indicate a highly significant improved survival for clinical stage I (CS-I) patients with lymph node metastases who received elective lymphadenectomy (ELND) *versus* clinical stage II (CS-II) patients who received therapeutic lymphadenectomy (TLND).[1,4] Five- and ten-year survival for ELND was 59% and 51% *versus* 43% and 38%, respectively, for TLND. This fact forms the basis for the frequent recommendation of ELND in patients with intermediate-depth primary melanomas.[26] On initial examination, however, almost 90% of melanoma patients have localized disease without clinical evidence of metastases to the regional lymph nodes or distant sites. Such CS-I patients present a common therapeutic dilemma regarding the management of the regional nodes. Some oncologists advise immediate ELND for these patients. Others adopt a program of "watch and wait" with careful follow-up examinations and delayed TLND if metastases develop, because such a small proportion of CS-I patients have microscopic metastases present in the regional nodes. Thus the benefit of ELND for patients who are CS-I is controversial. Most large, long-term, retrospective, biostatistical studies from single institutions have demonstrated a small but significant therapeutic benefit from ELND for patients with CS-I melanomas of an intermediate Clark's level or Breslow thickness.[27,28] Furthermore the survival rates after TLND average 15% to 25% higher for patients who are CS-I with clinically occult metastases to the regional lymph nodes (pathological stage II, PS-II) than for patients who are CS-II, a fact we have confirmed in this study (Fig. 1). This suggests that such CS-I and PS-II patients may benefit from early ELND.

In spite of this apparent benefit of ELND, randomized clinical trials have not demonstrated a statistically significant overall survival advantage from ELND for all patients with CS-I melanoma.[29–32] Even the randomized trial by the World Health Organization, however, found that patients with intermediate level melanoma of the extremities who underwent ELND had survival rates approximately 11% higher than patients who underwent delayed TLND.[30–32] This difference was not statistically significant

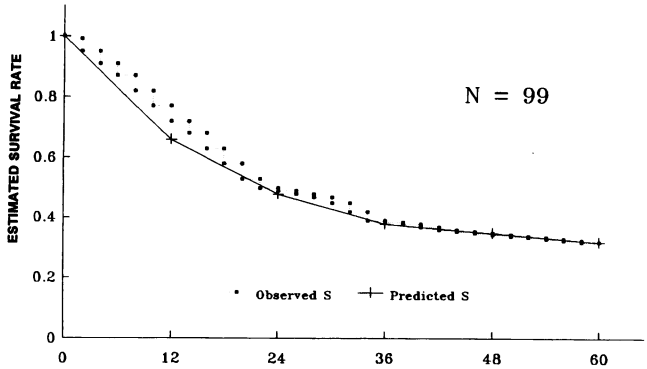

FIG. 7. Observed and predicted survival rates for high-risk group.

because there were small numbers of patients in this subset of the trial. Biostatistical considerations require the comparison of large numbers of patients to test the null hypothesis. Two such large, randomized trials are currently under way,[28] but the results will not be available for many years.

Intraoperative Lymphatic Mapping and Selective Lymphadenectomy

We have developed a method to identify, within the total population of CS-I melanoma patients, those who have nodal metastases, because they are the only ones that can benefit from ELND. In 1977 we introduced cutaneous lymphoscintigraphy[15-17] as a methodology for identifying the regional lymph basin of primary drainage for melanomas located in ambiguous sites, such as the midline of the trunk or the shoulder. We hypothesized that new operative techniques developed to identify the lymphatic drainage path from the site of the primary melanoma to the individual lymph nodes within the lymphatic basin might indicate those nodes most likely to contain metastatic melanoma. We have previously described our studies of intraoperative mapping of the regional lymphatics and demonstrate the procedure's high degree of accuracy in identifying those patients who have metastases in the regional lymph nodes.[33,34] Intraoperative mapping permits selective lymphadenectomy of sentinel draining lymph nodes, intraoperative frozen section, and immunohistochemistry, resulting in accurate pathologic staging. Thus surgeons can select those patients who are PS-II for immediate therapeutic lymph node dissection.

Using these techniques we have found that only 20% of CS-I melanoma patients have micrometastases to the regional lymph nodes that are detectable either by routine hematoxylin and eosin staining or by special immunohistochemical techniques. This 20% of patients then can be subjected to standard lymphadenectomy, whereas the other 80% of patients without nodal metastases can avoid the complications of radical lymphadenectomy.

We were surprised by the great heterogeneity in survival rates among patients with lymph node metastases, because our prejudice was that most factors were of little importance except for the tumor burden, as judged by the numbers of involved nodes and their clinical status. Our results indicate, however, that multiple prognostic factors are involved and must be considered in providing prognostic advice to each patient. The mathematical model that we have derived appears to be remarkably accurate in predicting survival of the various subsets of patients in our large data set. The most critical question, however, relates to the general applicability of this model to other data sets. This needs to be accomplished before it can be used for analysis of risk for adjuvant trials or prognosis of individual patients. We are optimistic that the combination of clinical pathologic features as quantitated by our model can be combined with certain serum markers of immunoprognostic importance that we have developed to predict more accurately the natural history of this erratic disease in an individual patient.[35] Unfortunately in a retrospective analysis of this type many features of the primary lesion, such as Balch's ulceration, mitotic index, or lymphocytic infiltration, could not be adequately evaluated. We expect this will be remedied by a detailed prospective evaluation of such factors currently under way by Dr. Alistair J. Cochran.

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Discussion

Dr. John Daly (Philadelphia, Pennsylvania): Thank you, Dr. Thompson. Malignant melanoma is a disease that is increasing in frequency in the United States of America. But fortunately it appears as though both earlier stages and thinner lesions are being identified.

Dr. Morton and his group should be complimented on developing this mathematical model that may predict survival in patients with pathologically involved regional lymph nodes. Interestingly despite the fact that these are cases that already have metastatic disease, they have noted that characteristics of the primary, such as thickness, and patient characteristics such as gender, and the site of location of the primary continue to be important survival predictors. This probably explains the tremendous heterogeneity of survivorship in this series, from 76% to 14%.

He and his group also should be complimented on their use of node mapping, because it is a major contribution, and I think it will allow us to test various concepts of elective nodal dissection with much less morbidity.

I have several questions. In the manuscript you noted that the 5-year survivorship of patients in this series was 46%, compared with an earlier series of 37%. Is this due to a more biologically favorable group of patients such as we have seen with colon cancer, for example? Or is there some other cause? It did not appear as though adjuvant immunotherapy was borne out to be effective by the univariate analysis.

Second is there any explanation as to why the site of location continues to be a major predictor of survival, even though we are talking about cases that have already metastasized to regional lymph nodes?

Third you noted that synchronous and nonsynchronous metastases are not different, but is time to the development of nodal metastasis important? In the patient who develops nodal mets 3, 4, or 5 years after the primary has been resected, do they have a better survival?

Finally have you had the opportunity to prospectively test your model in a group of patients that were not actually included in the model that you developed?

Dr. G. Aranha (Maywood): Does your scan identify those patients with intransit metastases? If it does, would removal of these metastases at the time of simultaneous node dissection and wide excision of the primary further improve your survival rates?

Dr. J. B. Aust (San Antonio, Texas): This is a continuing report by Dr. Morton's group, who have long tilled in the vineyard of malignant melanoma, the chameleon of malignancies, with its bizarre course from patient to patient.

They present a very large database, and extensive statistical analysis of risk factors leading to a mathematical formula that forecasts prognostic risks. I would not touch that formula with a 12-foot pole. It is probably statistically sound, but it looks very difficult to apply.

The previous study had a poorer prognosis than the present study, and one worries that retrospective data may not forecast the future results of the next series of patients. There may be other factors, however, that account for the current better results.

One, the disease may have changed. I really doubt that has occurred. We see more patients and we see them earlier, but I do not think the disease itself has changed.

Two, patients may be getting better treatment, because we are seeing the patients earlier and operating earlier on them. It is certainly not because of effective immunotherapy or chemotherapy, because these modalities have not proved to be of significant benefit in malignant melanoma.

The third factor is probably the most important one, better classification. We may be moving a number of previous early stage cases into a more advanced stage. Dr. Morton's techniques of mapping and perhaps better pathologic examination of excised lymph nodes all tend to produce more lymph-node-positive cases than there were in the previous group, reducing the number of stage I cases and increasing the number of stage II with patients of lesser tumor burden, thereby improving the reported results of both stages.

So I think that what may be happening is that they are improving the final results by restaging the patients in a more effective way, and not because of better therapy.

I would like Dr. Morton to address that particular issue, and I wish him well in his continued studies. He has been one of the senior investigators of malignant melanoma over a number of years.

Dr. Edward Krementz (New Orleans, Louisiana): President Thompson, I take this occasion to rise to discuss Dr. Morton's report of his vast experience with melanoma in southern California. With the rising rates of melanoma in this country, he will soon be able to report more cases than the Australians.

I am concerned about the present tendency for surgeons to discount the good effects of chemotherapy, and particularly those obtained by regional chemotherapy. When I started in practice over 40 years ago, just about all of the solid tumors treated with chemotherapy were treated by surgeons. Now with the increasing numbers of medical oncologists, this case material is largely being referred to that group. Even in the field of regional chemotherapy, we are losing some of these patients to the interventional radiologists working with the medical oncologists.

Our group has treated over a thousand patients with limb melanomas