# Prognostic Factors in Patients With Melanoma Metastatic to Axillary or Inguinal Lymph Nodes

## *A Multivariate Analysis*

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**Although pathologic nodal status is a major determinant of outcome in melanoma, there is substantial prognostic heterogeneity among node-positive patients. This study was undertaken to further clarify significant variables predicting survival in patients with melanoma metastatic to axillary or groin nodes. From 1019 patients with melanoma undergoing axillary or groin dissection between 1974 and 1984, the authors identified 449 patients with histologically positive nodes. Both univariate and multivariate analyses were performed using the Kaplan-Meier product limit method and the Cox model of proportional hazard regression. The major determinant of survival was pathologic stage (PS) according to the 1983 AJCC staging system. Three hundred fifty patients (78%) were classified PS-III (one nodal group involved), with a survival of 39% at 5 years and 32% at 10 years. Factors independently predictive of a favorable outcome in these patients were nontruncal primary site (p = 0.0002), microscopic nodal involvement (p = 0.001), number of positive nodes less than three (p = 0.003), and absence of extranodal disease (p = 0.01). Ninety-nine patients (22%) were classified PS-IV, 51 with two nodal stations involved (N2), 25 with intransit disease and one nodal station involved (N2), 7 with extraregional soft tissue metastases (M1), and 16 with visceral metastases (M2). Survival for PS-IV patients was 9% at 5 and 10 years, respectively. Within PS-IV, factors independently predictive of a more favorable outcome were the absence of extranodal disease (p = 0.0001), female sex (p = 0.03), and a long interval from diagnosis to lymph node dissection (p = 0.04). These factors were incorporated into a model predicting relative risk of death from disease for both PS-III and PS-IV patients, separating patients into groups at high, intermediate, and low risk of recurrence after lymphadenectomy.**

ALTHOUGH THE PATHOLOGIC nodal status is a primary determinant of outcome in patients with malignant melanoma, the risk of recurrence and death in these patients is quite variable and has been reported to range between 20% and 93%.[1,2] A number of reports have appeared over the last 10 years looking at prognostic factors in these patients. Patient-related factors that have been identified by multivariate analysis as independently significant predictors of recurrence and death include patient age and sex[3] and clinical stage.[4,5] Primary tumor-related variables identified as independently predictive of outcome include site,[3,5,6] Breslow thickness,[1,3,4,7,8] Clark level,[4] ulceration,[9] growth pattern,[10] and lymphocyte infiltration.[1] Lymph node-related variables identified include the number of positive lymph nodes,[3,5,9,10] the percent of positive lymph nodes,[1,6,8] and the presence of extranodal soft tissue extension of tumor.[6,10]

The current study was undertaken to reevaluate published prognostic factors and to attempt to develop a prognostic index incorporating those factors found to be significant by multivariate analysis. This index is intended to stratify patients into groups at high, intermediate, and low risk of recurrence, both to improve patient care and to identify more homogeneous groups of patients for inclusion into investigational adjuvant therapy trials. Furthermore identification of dominant prognostic variables by multivariate analysis may help to refine a uniform staging system for patients with melanoma metastatic to regional nodes such that cooperative trials pooling information from multiple centers can be meaningfully analyzed.

## Methods

### *Variables*

The analysis included patient-related variables of age, sex, clinical, and pathologic stage according to the 1983 American Joint Commission on Cancer (AJCC) staging system,[11] and interval from the diagnosis of melanoma to documentation of the positive nodes.

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Primary tumor-related variables included site (upper extremity, lower extremity, trunk, unknown), Clark level, Breslow thickness, AJCC T stage, and ulceration (present or absent). A broad definition of primary ulceration was employed; this was deemed present if there was a history of the primary lesion bleeding after minor trauma.

Lymph-node–related variables recorded included the number of positive nodes, the presence of extranodal soft tissue disease in the lymphadenectomy specimen, the status of the highest lymph node dissected (positive or negative), the size of the largest positive node removed (in centimeters), and the site of the positive nodes (axilla or groin). The extent of nodal involvement also was recorded; if neither the operating surgeon nor the pathologist described evidence of grossly visible metastatic disease, but tumor was subsequently found on histologic examination, the node was classified as microscopically positive. If either surgeon or pathologist described a grossly positive node that subsequently was confirmed histologically, the node was classified as macroscopically positive.

All patients were staged both clinically and pathologically according to the 1983 AJCC system (Table 1). This system classifies patients with clinically negative nodes as stage I (<1.5 mm thick, Clark I–III) and stage II (>1.5 mm thick, Clark IV–V). Patients with positive nodes in one nodal basin only, without intransit disease, are classified stage III. Patients with metastatic disease in more than one nodal basin, one nodal basin with evidence of intransit disease, or with any evidence of systemic disease are classified as stage IV.

TABLE 1. *American Joint Commission on Cancer Staging System for Melanoma*

| | |
|---|---|
| Primary tumor | |
| TX Unknown, cannot assess | |
| T0 Atypical melanocytic hyperplasia, in situ, Clark I | |
| T1 Clark II, ≤ 0.75 mm | |
| T2 Clark II, 0.76–1.50 mm | |
| T3 Clark IV, 1.51–4.0 mm | |
| T4 Clark V, > 4.0 mm or satellites within 2 cm of primary tumor | |
| Lymph nodes | |
| NX Unknown, cannot assess | |
| N0 Negative | |
| N1 One regional node station, nodes mobile, ≤ 5 cm diameter, or negative nodes and < 5 in-transit metastases | |
| N2 More than one node Station positive, nodes > 5 cm or fixed, > 5 in-transit metastases, or any in-transit metastases with positive nodes | |
| Distant metastases | |
| MX Unknown, cannot assess | |
| M0 None | |
| M1 Skin or subcutaneous tissue beyond the primary nodal area | |
| M2 Visceral | |
| Stage grouping | |
| Stage IA | T1, N0, M0 |
| Stage IB | T2, N0, M0 |
| Stage IIA | T3, N0, M0 |
| Stage IIB | T4, N0, M0 |
| Stage III | Any T, N1, M0 |
| Stage IV | Any T, N2, M0 or any T, any N, M1–2 |

The 1983 AJCC system classified patients with nodes greater than 5 cm in diameter as N2, thus stage IV. We have not found size of the largest node, when recorded, to be a significant prognostic variable, either by univariate or multivariate analysis.[6] In addition size of the largest node was recorded in only 192 of 449 patients (43%), with an equal size distribution seen between PS-III and PS-IV patients. For these reasons size of the largest node was not used to pathologically stage the patients in this review.

### *Operations Performed*

During the time of this review at our institution, elective node dissection was offered to patients in good general health with primary melanomas greater than or equal to Clark III, or more recently, greater than or equal to 1.5 mm in thickness. This treatment philosophy was based on the biostatistical prevalence of occult positive nodes in these patients and the suggestion of a survival benefit from elective node dissection in these patients as reported by a number of published retrospective studies.[12–15] In the case of axillary dissection, whether elective or therapeutic, the standard radical lymphadenectomy was performed, removing the entire axillary contents, usually including the pectoralis minor muscle, up to and including the level 3 nodes medial to the pectoralis minor, exposing the costoclavicular ligament. Groin dissection also followed well-established surgical techniques. Elective groin dissection usually consisted of a radical superficial inguinofemoral lymphadenectomy. Radical superficial and deep iliac/obturator dissection to the level of the aortic bifurcation usually was undertaken in the case of a therapeutic groin dissection for clinically positive nodes.

### *Adjuvant Therapy*

In general patients with positive nodes, no evidence of extranodal disease (*i.e.*, pathologic stage III), and no medical contraindications were offered participation in one of a series of sequential phase I adjuvant vaccine trials investigating the response to a number of modified radiated autologous or allogeneic melanoma whole cell vaccines. As these were uncontrolled nonrandomized trials where the end point was detection of serologic titers or assessment of cell-mediated cytotoxicity, no statement can be made as to the impact of these trials on survival in participating patients. Of note, however, during this period only an occasional vaccinated patient demonstrated any serologic response or increase in cell-mediated cytotoxicity after receiving the whole cell vaccine. This prompted a shift to the investigation of adjuvant vaccination using purified melanoma antigens at our institution in the years after 1985.

*Survival*

Survival was determined from both the date of diagnosis and the date of lymph node dissection to the date of death or last follow-up, in an attempt to take into account the lead time bias in survival accrued to patients undergoing lymph node dissection earlier in the course of their melanoma. As results were similar when analyzed by both methods, survival is reported as the interval from the date of lymph node dissection, as this is the point common to all patients when all pathologic material was available for review and pathologic staging. Survival for each variable was estimated for each variable by the product-limit method of Kaplan and Meier.[16] Survival distributions were compared using the log-rank method as described by Mantel.[17]

Proportional hazards regression was used to incorporate all of the explanatory variables in the same model.[18] Forward stepwise procedure and likelihood ratio tests were used to select the variables with the greatest prognostic value. Interaction among the variables also was considered. The adequacy of the model to the data was checked by fitting separate proportional hazard models to partitions of the data determined by a given categorical variable. The coefficients estimated by each partition should not differ substantially unless there was an interaction effect. Cumulative hazard plots also were generated to visually check the assumption of the proportionality of the hazard rates.

The statistical analysis was performed using the BMDP statistical package.[19] Differences were considered significant at the $p = 0.05$ level.

## Results

The records of 1019 patients with melanoma undergoing axillary or inguinal lymph node dissection at Memorial Sloan-Kettering Cancer Center between 1974 and 1984 were reviewed; 449 (44%) were found to have histologically confirmed metastatic melanoma in regional nodes. There were 261 male and 188 female patients. The median age was 50 years (range 8–84 years). The location of the primary lesion was upper extremity in 47 patients, lower extremity in 168 patients, and trunk in 183 patients. In 51 patients the site of the primary lesion was occult.

The distribution of clinical and pathologic staging is shown in Table 2. Of the 449 patients with positive nodes, 102 (23%) had been classified as clinical stage I to II, in other words, with clinically negative nodes; these patients underwent elective lymph node dissection (ELND). Two hundred seventy-four patients (61%) were classified as clinical stage III, with clinically positive nodes in the absence of extraregional disease, and underwent therapeutic lymph node dissection (TLND). In the remaining 73 patients (16%) classified as clinical stage IV, the lymph node dissection was termed palliative (PLND), intended for locoregional control of disease in patients with more than one nodal group involved, or with evidence of extranodal metastases. Included in this group, as defined by the 1983 AJCC staging system, were 28 patients with metastases in more than one nodal group (N2), 22 patients with nodal metastases to one nodal group and intransit metastases (N2), 7 patients with extraregional soft tissue metastases (M1), and 16 patients with visceral metastases (M2).

TABLE 2. *Clinical and Pathologic Stages*

| | Pathologic Stage | | |
|---|---|---|---|
| Clinical Stage | III | IV | All |
| I, II | 96 | 6 | 102 |
| III | 254 | 20 | 274 |
| IV | 0 | 73 | 73 |
| ALL | 350 | 99 | 449 |

Of the 449 patients, 147 (33%) were found to have positive nodes within 1 month of the diagnosis of melanoma. The majority of patients in this subgroup underwent elective lymph node dissection for clinically negative nodes (66 patients) or therapeutic lymph node dissection for metastatic melanoma of unknown primary (25 patients). Another 147 patients (33%) were found to have positive nodes from 1 to 9 months after the initial diagnosis of melanoma. One hundred fifty-five patients (34%) were found to have positive nodes more than 6 months subsequent to the diagnosis and treatment of their primary melanoma, at a median delay of 32 months (range, 9–449 months).

Median follow-up for the 298 patients dead of disease was 21 months, and 84 months for the 130 patients alive and free of disease at the time of analysis. Eight patients were alive with disease at a mean of 82 months' follow-up, and nine patients had died of other causes at a mean of 40 months' follow-up. Only four patients were lost to follow-up, three of them having returned abroad immediately after lymphadenectomy.

*Survival*

Overall survival for the entire group is shown in Figure 1. The estimated median survival was 27 months, with a 5-year survival (5YS) of 32% and a 10-year survival (10YS) of 27%. The single most important predictor of outcome in these node-positive patients was pathologic stage (PS). For the 350 PS-III patients, the median survival was 38 months, with a 5YS of 39% and a 10YS of 32%. For the 99 PS-IV patients the median survival was 11 months, with a 5YS and 10YS of 9% ($p < 0.0001$). Because these groups were so clinically disparate, they were separated for the purposes of subsequent detailed analysis.

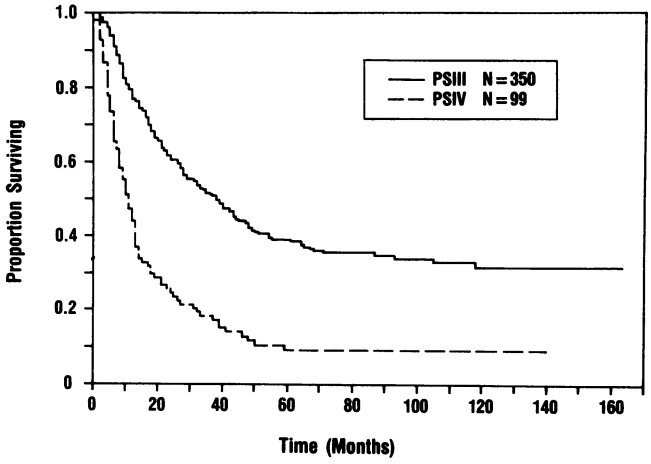


FIG. 1. Overall survival of 449 patients with melanoma metastatic to axilla or groin by pathologic stage.

### *Pathologic Stage III—Univariate Analysis*

The distribution and outcome of PS-III patients stratified by univariate analysis of patient-related factors, primary related factors, and lymph-node–related factors is shown in Tables 3, 4, and 5.

Of the patient-related factors, low clinical stage predicted a more favorable outcome; patients with clinically negative nodes (*i.e.*, CS-I, CS-II) had a better outcome than those with clinically positive nodes ($p = 0.003$). The timing of lymph node dissection (LND) relative to diagnosis was also an important factor ($p = 0.02$), with patients undergoing LND from 1 to 9 months after diagnosis faring worse than those undergoing LND within a month of diagnosis (mostly elective node dissections for clinically occult disease) or those undergoing LND more than 9 months after diagnosis (perhaps with biologically more indolent tumors). Age and sex were not predictive of outcome in PS-III patients.

Of the primary related variables, nontruncal site was the most highly predictive of outcome ($p = 0.0004$ *vs.* truncal site). Clark level was also significant because of the very poor outcome of patients with Clark V primaries ($p = 0.02$). This survival difference was not observed in those patients in whom the Breslow thickness was known to be greater than 2.5 mm and was not seen when Clark level and Breslow thickness were combined into the category of AJCC T stage. Ulceration of the primary was not significant.

The most important variables were related to characteristics of the positive nodes. The extent of nodal involvement (macroscopic *vs.* microscopic) and the presence or absence of extranodal soft tissue extension of tumor in the lymphadenectomy specimen were highly predictive of outcome ($p < 0.0001$). The number of positive nodes was also highly significant ($p = 0.0007$). Finally, as expected, those patients in whom the highest node dissected was positive had a poorer survival than those in whom the highest node was negative ($p = 0.001$). Factors not predictive of outcome in this group included the size of the largest positive node and the site of lymphadenectomy.

### *Pathologic Stage III—Multivariate Analysis*

All of the variables included in the univariate analysis were entered into a forward stepwise proportional hazards regression. Complete information on all variables was available on 308 of the 350 patients. Table 6 shows the summary of the multivariate analysis in terms of likelihood ratio tests, regression coefficients, and standard errors of the selected variables. No other variables showed

TABLE 3. *Univariate Analysis of Patient-Related Factors: Pathologic Stage III*

| Variable | N | Median Survival (mo) | 5-Year Survival (%) | 10-Year Survival (%) | p (Mantel–Cox) |
|---|---|---|---|---|---|
| Sex | | | | | |
| M | 206 | 38 | 39 | 32 | |
| F | 144 | 42 | 43 | 37 | 0.41 |
| Age (yr) | | | | | |
| <44 | 117 | 44 | 47 | 40 | |
| 44–57 | 120 | 35 | 37 | 34 | |
| >57 | 113 | 35 | 36 | 29 | 0.33 |
| Clinical stage | | | | | |
| IB | 9 | — | 86 | 68 | |
| IIA | 57 | 87 | 52 | 41 | |
| IIB | 30 | 54 | 40 | 36 | |
| III | 254 | 29 | 35 | 31 | 0.003 |
| Delay to LND | | | | | |
| ≤1 mo | 123 | 47 | 45 | 38 | |
| 1–9 mo | 117 | 26 | 32 | 27 | |
| >9 mo | 110 | 44 | 43 | 38 | 0.02 |

LND, lymph node dissection.

TABLE 4. *Univariate Analysis of Primary-Related Variables: Pathologic Stage III*

| Variable | N | Median Survival (mo) | 5-Year Survival (%) | 10-Year Survival (%) | p (Mantel–Cox) |
|---|---|---|---|---|---|
| Site | | | | | |
| Arm | 43 | 64 | 54 | 46 | |
| Leg | 125 | 48 | 46 | 37 | |
| Trunk | 145 | 27 | 28 | 23 | |
| Unknown | 37 | 35 | 46 | 39 | |
| Nontrunk | 205 | 48 | 47 | 38 | 0.0004 *vs.* trunk |
| Level | | | | | |
| II | 22 | 38 | 40 | 40 | |
| III | 79 | 42 | 40 | 38 | 0.016 |
| IV | 131 | 42 | 44 | 35 | |
| V | 20 | 16 | 0 | 0 | |
| Breslow thickness | | | | | |
| ≤2.5 mm | 84 | 40 | 40 | 35 | 0.94 |
| >2.5 mm | 86 | 39 | 40 | 34 | |
| AJCC T stage | | | | | |
| T1 | 21 | 38 | 37 | 37 | |
| T2 | 63 | 40 | 38 | 31 | |
| T3 | 135 | 42 | 42 | 36 | |
| T4 | 48 | 33 | 36 | 33 | 0.86 |
| Ulceration | | | | | |
| Absent | 195 | 42 | 40 | 33 | |
| Present | 98 | 38 | 42 | 38 | 0.85 |

AJCC, American Joint Commission on Cancer.

independent prognostic importance in the proportional hazards regression. The hypothesis that all of the regression coefficients were zero was rejected (chi square = 44.33, $df = 4$, $p < 0.00001$).

The four independently significant variables of extranodal disease, extent of nodal involvement, primary site, and number of positive nodes were incorporated into an equation to predict the relative risk of death from disease when all four variables were considered simultaneously. The risk equation is:

$$\text{RISK} = \text{Exp}(0.80E + 0.61M + 0.59T + 0.48N)$$

where

E = 1 if extranodal disease is present, E = 0 if extranodal disease is absent

M = 1 if nodes are macroscopically positive, M = 0 if nodes microscopically positive

T = 1 if primary site is truncal, T = 0 if primary site is nontruncal

N = 1 if >2 nodes are positive, N = 0 if ≤2 nodes are positive

If all factors are absent, the relative risk of dying of disease is 1. Figure 2 shows the survival curves of PS-III

TABLE 5. *Univariate Analysis of Lymph Node-Related Variables: Pathologic Stage III*

| Variable | N | Median Survival (mo) | 5-Yr Survival (%) | 10-Yr Survival (%) | p (Mantel–Cox) |
|---|---|---|---|---|---|
| No. of positive nodes | | | | | |
| 1 | 167 | 48 | 46 | 40 | |
| 2–3 | 92 | 44 | 45 | 40 | |
| >3 | 61 | 20 | 26 | 19 | 0.0007 |
| Extent of nodal involvement | | | | | |
| Microscopic | 83 | — | 63 | 52 | |
| Gross | 264 | 28 | 33 | 29 | 0.0000 |
| Extranodal extension | | | | | |
| Absent | 313 | 43 | 43 | 36 | |
| Present | 34 | 11 | 16 | 16 | 0.0000 |
| Largest positive node | | | | | |
| <2 cm | 63 | 40 | 39 | 39 | |
| 2–3 cm | 44 | 47 | 41 | 35 | |
| >3 cm | 25 | 19 | 22 | 22 | 0.15 |
| Highest node status | | | | | |
| Negative | 294 | 43 | 44 | 37 | |
| Positive | 16 | 11 | 19 | 19 | 0.001 |
| Site of lymph node dissection | | | | | |
| Axilla | 195 | 28 | 36 | 31 | |
| Groin | 155 | 43 | 43 | 33 | 0.15 |

TABLE 6. *Final Proportional Hazard Regression Model: Pathologic Stage III. Variables of Prognostic Importance*

| Variable | Likelihood Ratio Test (p) | Regression Coefficient (SE) |
|---|---|---|
| Gross appearance | 0.0010 | 0.608 (0.195) |
| Truncal primary | 0.0002 | 0.595 (0.158) |
| > 2 positive nodes | 0.0029 | 0.479 (0.157) |
| Extranodal disease | 0.0098 | 0.804 (0.285) |

patients stratified by relative risk as determined by these variables. The difference in survival between patients with a risk of >2 compared with ≤2 is highly significant ($p < 0.0001$), and clearly separates pathologic stage III patients into groups at low and high risk of recurrence and death from disease after axillary or inguinal node dissection.

*Pathologic Stage IV—Univariate Analysis*

The distribution and outcome of PS-IV patients stratified by univariate analysis of patient-related factors, primary related factors, and lymph-node–related factors are shown in Tables 7, 8, and 9.

Of the patient-related variables, only female sex predicted a more favorable outcome ($p = 0.01$). Of interest when the survival of these patients was examined by why they were classified as stage IV, there was no significant difference comparing the patients with more than one positive node group, the patients with visceral metastases, and the patients with positive nodes and intransit disease. There was a trend toward a more favorable outcome in patients with extraregional skin or soft tissue metastases, but this was not statistically significant ($p = 0.11$).

None of the primary related factors was a significant predictor of outcome in the PS-IV patient group.

Of the lymph-node–related variables, the presence or absence of extranodal soft tissue disease strongly influenced prognosis ($p < 0.0001$). Macroscopic nodal appearance approached statistical significance as a predictor of outcome ($p = 0.06$).

*Pathologic Stage IV—Multivariate Analysis*

All of the variables included in the univariate analysis were entered into a forward stepwise proportional hazards regression. Complete information on all variables was available on 98 of the 99 patients. Table 10 shows the summary of the multivariate analysis in terms of likelihood ratio tests, regression coefficients, and standard errors of the selected variables. No other variable showed independent prognostic importance in the proportional hazards regression. The hypothesis that all the regression coefficients were zero was rejected (chi square = 26.48, $df = 3$, $p < 0.00001$).

The three independently significant variables of extranodal disease, sex, and interval from diagnosis to lymph node dissection were incorporated into an equation to predict the relative risk of death from disease when all three variables were considered simultaneously. The risk equation is:

$$\text{RISK} = \text{Exp}(0.97E + 0.48S - 0.004D)$$

where

E = 1 if extranodal disease is present, E = 0 if extranodal disease is absent
S = 1 if sex is male, S = 0 if sex is female
D = interval from diagnosis of melanoma to lymph node dissection in months

Figure 3 shows the survival curves of PS-IV patients by relative risk of dying as determined by these factors. The survival difference between those patients with a risk of ≤1 compared with those with a risk > 1 is highly significant ($p < 0.0001$). Clearly the presence of any one of the major risk factors, either extranodal disease or male sex, and to a lesser extent, a short interval from diagnosis to lymph node dissection (portending a biologically more aggressive tumor) predicts a very poor outcome.

*Recurrence*

Of the 449 patients with positive axillary or inguinal nodes, 300 (67%) recurred. The time to first recurrence is shown in Figure 4. Of note 50% of all recurrences had become manifest by 8 months. By 2 years after lymphadenectomy, 85% of the risk of recurrence had passed.

## Discussion

These data confirm the observations of other investigators that there is broad prognostic variability among

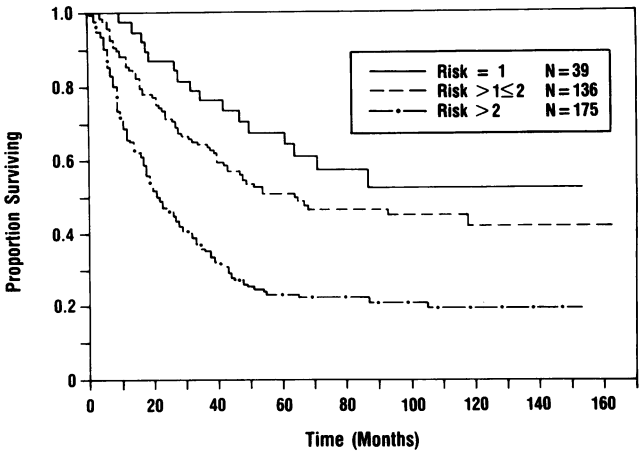


FIG. 2. Survival of 350 patients with melanoma metastatic to axilla or groin, pathologic stage III, by relative risk of death as determined by factors significant on multivariate analysis.

TABLE 7. *Univariate Analysis of Patient-Related Factors: Pathologic Stage IV*

| Variable | N | Median Survival (mo) | 5-Yr Survival (%) | 10-Yr Survival (%) | p (Mantel–Cox) |
|---|---|---|---|---|---|
| Sex | | | | | |
| M | 55 | 9 | 5 | 5 | |
| F | 44 | 13 | 15 | 15 | 0.01 |
| Age (yr) | | | | | |
| <44 | 32 | 13 | 15 | 15 | |
| 44–57 | 28 | 10 | 7 | 7 | |
| >57 | 39 | 8 | 9 | 9 | 0.19 |
| Clinical stage | | | | | |
| IB | 1 | — | — | — | |
| IIA | 2 | 32 | 0 | 0 | |
| IIB | 3 | — | 67 | 67 | |
| III | 20 | 12 | 0 | 0 | |
| IV | 73 | 10 | 9 | 9 | 0.11 |
| Delay to LND | | | | | |
| ≤1 mo | 24 | 10 | 8 | 8 | |
| 1–9 mo | 30 | 10 | 10 | 10 | |
| >9 mo | 45 | 11 | 9 | 9 | 0.84 |
| Why stage IV | | | | | |
| N2 | 51 | 8 | 7 | 7 | |
| M1 | 7 | 50 | 38 | 38 | |
| M2 | 16 | 8 | 7 | 7 | |
| NIN | 25 | 13 | 8 | 8 | 0.11 |

LND, lymph node dissection; N2, two nodal groups involved; M1, extraregional skin/soft tissue metastases; M2, visceral metastases; NIN, positive nodes with in-transit metastases.

patients with melanoma metastatic to regional nodes. In fact we are reminded that the presence of nodal metastases, although important, does not constitute a categorical variable, either present or absent. Rather it defines another segment of the prognostic spectrum whose most important components are indicators of tumor burden (more than one node basin involved, extranodal disease, macroscopic nodal involvement, multiple nodes involved).

### *AJCC Staging*

The 1983 AJCC Staging system grouped patients with metastatic disease in more than one nodal basin in the absence of clinically evident systemic metastases (N2) with those with nodal metastases and soft tissue or visceral metastases (M1, M2) into stage IV, prognostically quite distinct from patients with nodal metastases to one nodal

TABLE 8. *Univariate Analysis of Primary-Related Variables: Pathologic Stage IV*

| Variable | N | Median Survival (mo) | 5-Yr Survival (%) | 10-Yr Survival (%) | p (Mantel–Cox) |
|---|---|---|---|---|---|
| Site | | | | | |
| Arm | 4 | 5 | 0 | 0 | |
| Leg | 43 | 13 | 8 | 8 | |
| Trunk | 38 | 9 | 11 | 11 | |
| Unknown | 14 | 10 | 7 | — | |
| Nontrunk | 61 | 13 | 8 | 8 | 0.15 *vs.* trunk |
| Clark level | | | | | |
| II | 5 | 13 | 0 | 0 | |
| III | 12 | 14 | 25 | 25 | |
| IV | 32 | 7 | 0 | 0 | |
| V | 9 | 13 | 0 | 0 | 0.08 |
| Breslow thickness | | | | | |
| ≤2.5 mm | 10 | 13 | 15 | 15 | |
| >2.5 mm | 20 | 8 | 10 | 10 | 0.39 |
| AJCC T stage | | | | | |
| T1 | 5 | 13 | 0 | 0 | |
| T2 | 12 | 13 | 25 | 25 | |
| T3 | 31 | 8 | 5 | 5 | |
| T4 | 17 | 11 | 0 | 0 | 0.26 |
| Ulceration | | | | | |
| Absent | 57 | 10 | 13 | 13 | |
| Present | 22 | 12 | 4 | 4 | 0.15 |

AJCC, American Joint Commission on Cancer.

TABLE 9. *Univariate Analysis of Lymph Node-Related Variables: Pathologic Stage IV*

| Variable | N | Median Survival (mo) | 5-Yr Survival (%) | 10-Yr Survival (%) | p (Mantel–Cox) |
|---|---|---|---|---|---|
| No. of positive nodes | | | | | |
| 1 | 13 | 10 | 23 | 23 | |
| 2–3 | 19 | 24 | 11 | 11 | |
| >3 | 32 | 9 | 6 | 6 | 0.09 |
| Extent of nodal involvement | | | | | |
| Microscopic | 5 | 32 | 40 | 40 | |
| Gross | 93 | 11 | 8 | 8 | 0.06 |
| Extranodal extension | | | | | |
| Absent | 62 | 13 | 15 | 15 | |
| Present | 36 | 6 | 0 | 0 | 0.0000 |
| Largest positive node | | | | | |
| <2 cm | 18 | 9 | 0 | 0 | |
| 2–3 cm | 17 | 10 | 6 | 6 | |
| >3 cm | 25 | 9 | 8 | 8 | 0.85 |
| Highest node status | | | | | |
| Negative | 49 | 11 | 10 | 10 | |
| Positive | 29 | 8 | 14 | 14 | 0.67 |
| Site of lymph node dissection | | | | | |
| Axilla | 30 | 10 | 17 | 17 | |
| Groin | 69 | 11 | 5 | 5 | 0.69 |

basin only (N1). This stage grouping was fully validated by our analysis. As shown in Table 7, there was no significant difference in survival by why the patients were classified PS-IV. In fact pathologic stage was such an important predictor of outcome in this review that PS-III and PS-IV patients were analyzed separately.

*Pathologic Stage III.* Within the group of patients classified as PS-III, with metastases to only one nodal basin, factors reflecting tumor burden were most predictive of outcome. The presence of extranodal tumor extension, macroscopic as opposed to microscopic nodal involvement, and a high number of positive nodes all predicted early recurrence and death. This is consistent with data reported from a number of prior studies of melanoma patients with nodal metastases, by both univariate[1,4,11,20–22] and multivariate[3,5–7,9,10] analysis.

Extracapsular extension of tumor into perinodal soft tissue has also been observed to be a predictor of recurrence and death in a number of other malignancies, including larynx,[23] breast,[24] and testis.[25]

In this review we found that prognosis deteriorated substantially when three or more nodes were involved. Other studies have reported this number to range from two to five nodes. Clearly as with the other indices of tumor burden, number of positive nodes is a continuous rather than a discrete variable, the risk of recurrence increasing with the number of nodes involved.

As we have shown previously,[6] size of the largest positive node was not a significant predictor of death, either within pathologic stage or when all patients were considered together. This is contrary to what would be predicted by the AJCC staging system in which patients with nodes greater than 5 cm in diameter are upstaged from N1 to N2.

Finally clinical stage, significant as a predictor of outcome by univariate analysis, was excluded from the final model, entirely overshadowed by these three pathologic factors.

The only non–lymph-node-related variable found to be significant was truncal as opposed to extremity or occult primary site. This has been observed by a number of prior investigators.[3,5,6] The explanation for this is not clear, but it does not appear to be related to the more indeterminate lymphatic drainage patterns of truncal primaries. The site of first relapse after treatment of truncal primaries is much more frequently systemic rather than in an undissected lymph node basin.[26] There may be an as yet unidentified indicator of the biologic aggressiveness that can help to define the more aggressive behavior of these axial melanomas.

The relative risk equation generated by incorporating the weighted contributions of each of the factors significant by multivariate analysis serves a number of purposes. As

TABLE 10. *Final Proportional Hazard Regression Model: Pathologic Stage IV. Variables of Prognostic Importance*

| Variable | Likelihood Ratio Test (p) | Regression Coefficient (SE) |
|---|---|---|
| Extranodal disease | 0.0001 | 0.967 (0.234) |
| Sex | 0.0293 | 0.479 (0.222) |
| Diagnosis to LND | 0.0375 | −0.004 (0.002) |

LND, lymph node dissection.

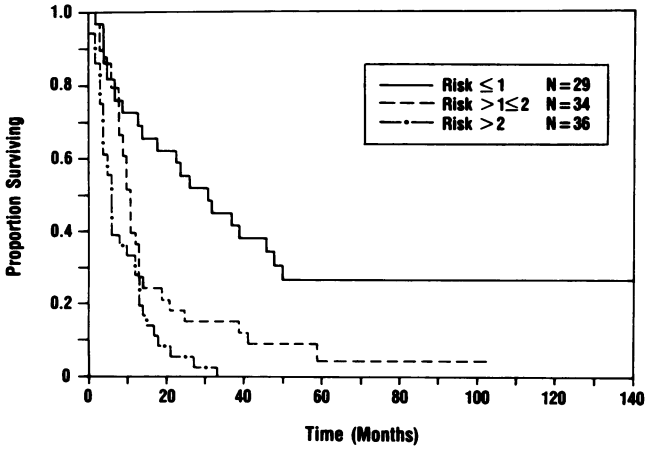


FIG. 3. Survival of 99 patients with melanoma metastatic to axilla or groin, pathologic stage IV, by relative risk of death as determined by factors significant on multivariate analysis.

shown in Figure 2, patients with none of the risk factors present (risk = 0) have a long-term disease-free survival of 54%. This is not the population that one would target for or even want to include in an aggressive surgical adjuvant trial. Conversely patients with a relative risk of greater than 2 have an 80% chance of relapse and death. With a median survival of only 18 months, this subset of PS-III patients would very quickly demonstrate the efficacy of a single-armed adjuvant program, prompting its more formal evaluation in a prospective randomized fashion.

*Pathologic Stage IV.* In this review, which focused only on patients with positive nodes, we could demonstrate no difference in survival among patients with metastases to more than one nodal basin (N2), those with nodal and intransit metastases (N2), and those with nodal and visceral metastases (M2). The trend toward improved survival in patients with nodal and soft tissue metastases (M1) has been noted previously,[27] although it was not statistically significant in our series. The very poor prognosis of N2 patients, including patients with metastases to bilateral axillary or superficial groin nodes, or to both superficial and deep inguinal nodes, emphasizes the importance of trying to develop novel aggressive surgical adjuvant programs.

Even within the subgroup of node-positive PS-IV patients, the presence of extranodal tumor extension was highly predictive of systemic failure. The prevalence of this factor alone could help to explain some of the discrepancy between results reported after groin dissection in patients with melanoma metastatic to inguinal and iliac or obturator nodes.[2,28]

Female sex was a favorable predictor of outcome in node-positive PS-IV patients. The influence of hormonal milieu on the course of patients with advanced melanoma has been long debated without resolution. Easier to explain is the favorable impact of a longer interval from diagnosis to lymph node dissection in these patients, as an indirect indicator of the biologic aggressiveness or "pace" of the disease in an individual patient.

The relative risk equation again combines the weighted contribution of each of these factors into an estimated probability of survival, as shown in Figure 3. This equation is clearly able to separate patients into a group at risk for very early recurrence and death from those who can anticipate a small but finite long-term probability of survival, independent of the presence or absence of visceral metastases.

*Recurrence*

The time to first recurrence plot, shown in Figure 4, has important implications with regard to the clinical management of node-positive melanoma patients. Although it is recognized that there is a subset of melanoma patients who will manifest their first recurrence 10 years or more after treatment of their primary, most of these patients will have had negative nodes at initial treatment.[29,30] In contrast half of patients in this series with positive nodes who recurred did so within 8 months. From the individual patient's standpoint, it is extremely reassuring to hear that by 1 year 70% of the risk of recurrence is passed, and that by 2 years 85% of the risk of recurrence is passed.

It is also helpful for the clinician to understand the time course of recurrent disease so that a rational schedule of follow-up can be developed. If one wishes to detect a 10% increment in cumulative risk of recurrence at each successive visit, then one would need to see the patient every 2 months for eight visits to detect the 80% cumulative risk of recurrence that occurs within the first 16

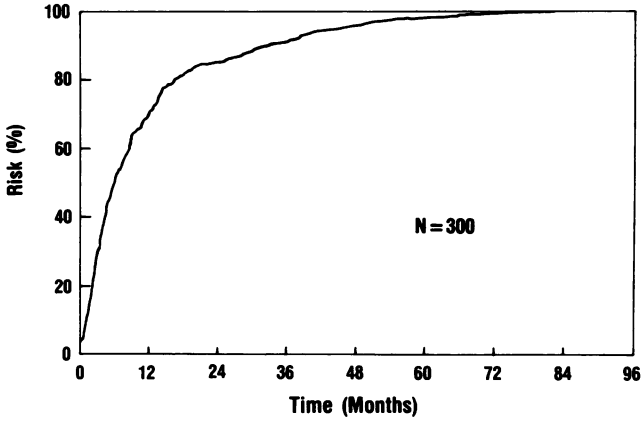


FIG. 4. Cumulative risk of recurrence over time in 300 patients whose disease recurred after lymphadenectomy for melanoma metastatic to axillary or groin nodes.

months. Clearly, however, as the slope of the recurrence curve flattens out after 2 years, follow-up could be arranged at much less frequent intervals.

## Summary

In summary long-term survival after resection of melanoma metastatic to axillary or inguinal nodes is clearly possible; this fact should negate any therapeutic surgical nihilism in these patients. These patients do represent an extremely heterogeneous population, however, one that can be subdivided into groups by pathologic stage, and within pathologic stage by a number of patient-, primary-, and lymph-node–related variables. Within pathologic stage III patients, we can clearly identify patients at high and low risk of recurrence based on the presence of extranodal disease, the extent of nodal involvement, the primary site, and the number of nodes involved. Even within pathologic stage IV, which should justifiably include all patients with N2 disease, patients at relatively higher and lower risk of recurrence can be identified, using the variables of extranodal disease, sex, and interval from diagnosis to lymph node dissection. This type of analysis clearly defines subgroups of patients who are at very high risk of recurrence and death, patients who should be offered participation in aggressive surgical adjuvant trials.

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