ORIGINAL ARTICLE

Clinical Node-Negative Thick Melanoma

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Background: Patients with T4 N0 M0 melanoma are considered at high risk for having occult metastases, and adjuvant therapy is usually recommended.

Hypothesis: Long-term survival in patients with thick melanoma is not universally poor.

Design: A retrospective study.

Setting: University teaching hospital.

Patients: We evaluated clinical node-negative thick (≥4.0 mm) melanoma in 151 patients who received their primary definitive surgical treatment in our department. None of these patients received any adjuvant therapy.

Results: Median follow-up was 44 months; median thickness, 5.5 mm. Median overall (OS) and disease-free survivals (DFS) were 70 (5-year survival, 52%) and 51 months (5-year survival, 47%), respectively. Patients with node-positive disease faired significantly worse than did those with node-negative disease. Median OS and DFS for patients with node-positive disease were 49 and 32 months (5-year survival, 35%), respectively, compared with 209 (5-year survival, 61%) and 165 months (5-year survival, 56%), respectively, for patients with node-negative disease. Similarly, OS and DFS were significantly lower when the primary tumor had at least 5 mitoses/mm^2 or was located in the head and neck region. After multivariate analysis, status of the lymph nodes was the most predictive variable for OS and DFS.

Conclusions: The thickness of melanoma, by itself, should not be used as a criterion for adjuvant therapy. Other prognostic factors should be considered.

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PATIENTS with thick (≥4.0 mm) melanoma have a high probability of occult metastases to the regional nodes (>60%) and to distant sites (>70%).[1,2] For this reason, adjuvant therapy rather than regional operation historically has been suggested for these patients.

This all-pervasive therapy recommendation prompted us to question whether all patients with thick melanoma will benefit from adjuvant therapy or whether a subset of patients in this group (eg, those without regional node involvement) will not require adjuvant therapy. Therefore, we analyzed the effect of nodal status on survival in our patients with thick melanoma. Since patients in this retrospective series underwent elective lymph node dissection (ELND) at the time of the primary treatment, the exact nodal status of our patients was known from the first day of initial treatment.

The objective of this analysis is to ascertain the natural history (ie, overall [OS] and disease-free survivals [DFS]) of patients with thick melanoma who were treated with surgery only. The results of this study would suggest whether use of adjuvant therapy enhances the OS or DFS of patients who have thick melanoma without clinical evidence of regional lymph node metastases (T4 N0 M0).

RESULTS

PATIENT CHARACTERISTICS

One hundred fifty-one patients underwent surgical treatment for thick melanoma during the study, including 84 male (55.6%) and 67 female (44.4%) patients. Their ages ranged from 13 to 89 years (mean age, 53.7 ± 16.6 years). Of these 151 patients, 121 underwent ELND.

TUMOR CHARACTERISTICS

The location of the primary tumor was in the lower extremity in 52 patients (34.4%),

PATIENTS AND METHODS

We identifed 151 consecutive patients with clinical node-negative thick melanomas in the University of Illinois at Chicago Department of Surgical Oncology registry from March 1, 1970, to August 31, 1995. All of these patients received surgical treatment from the faculty of the Department of Surgical Oncology; treatment consisted of wide excision of the primary lesions (2- to 5-cm margins). Complete regional ELND was performed simultaneously in 121 patients.[3] All histological material was examined by us. None of these patients received any form of adjuvant therapy.

Data on 151 patients were analyzed to evaluate the effect on OS and DFS of known prognostic variables such as age; sex; thickness, histological characteristics, and location of primary tumor; number of mitoses per square millimeter; and ulceration. We also analyzed the effect of nodal status on OS and DFS in the 121 patients who underwent ELND. We evaluated these variables using the Kaplan-Meier method with log-rank comparison. Multivariate analyses were performed using Cox regression analysis. Differences were considered significant at $P \leq .05$. Analyses were performed using SPSS computer software (SPSS Inc, Chicago, Ill). Death due to melanoma was considered the only event for OS. The DFS events included regional recurrences and distant metastases.

Patients with thick melanoma are followed up on a monthly basis for the first 2 years. They are then followed up every 3 months for 2 years, every 6 months for 2 years, and then on a yearly basis. We routinely obtain a chest x-ray film and perform liver function tests every 6 months during the first 2 postoperative years; after that, on a yearly basis. Further imaging studies are obtained depending on abnormal findings. Unless otherwise indicated, data are given as mean±SD.

Table 1. Clinical and Pathological Patient Characteristics*

Sex, No. (%)	
Male	84 (55.6)
Female	67 (44.4)
Age, y	
Mean ± SD	53.7 ± 16.6
Range	13-89
Thickness, mm	
Mean ± SD	6.6 ± 2.7
Range	4.0-17.5
Location of primary tumor, No. (%)	
Lower extremity	52 (34.4)
Trunk	46 (30.5)
Head and neck	28 (18.5)
Upper extremity	19 (12.6)
Perineum	6 (4.0)
Histological features of primary tumor, No. (%)	
Nodular	95 (62.9)
Superficial spreading	42 (27.8)
Acral lentiginous	12 (7.9)
Lentigo maligna	2 (1.3)
Ulceration, No. (%)	
Present	85 (56.3)
Absent	66 (43.7)
Mitoses per square millimeter, No. (%)	
<5	62 (41.0)
≥5	89 (58.9)
Nodal status, No. (%)†	
Positive	36 (29.7)
Negative	85 (70.2)

*Percentages have been rounded and may not total 100.
†One hundred twenty-one patients underwent elective lymph node dissection.

the trunk in 46 (30.5%), the head and neck in 28 (18.5%), the upper extremity in 19 (12.6%), and the perineum in 6 (4.0%) (**Table 1**). The mean tumor thickness was 6.6±2.73 mm (range, 4.0-17.5 mm; median, 5.5 mm). The most common histological finding of melanoma in this study group was nodular melanoma (95 patients [62.9%]). Forty-two patients (27.8%) had superficial spreading melanoma; 12 (7.9%), acral-lentiginous melanoma; and 2 (1.3%), lentigo maligna melanoma. Melanomas in 85 patients (56.3%) were ulcerated. We detected a mean of 6.17±4.12 per square millimeter (range, 1-31; median, 5).

Of the 121 patients who underwent ELND, 36 (29.8%) had node-positive disease. The mean number of positive nodes was 2.0 (median, 1.0; range, 1-13). Table 1 summarizes the patient and tumor characteristics.

SURVIVAL

The median follow-up was 44 months (range, 1-247 months). The OS and DFS were 70 (5-year survival, 52%) and 51 (5-year survival, 47%) months, respectively (**Figure 1**). The results of univariate analyses of several known prognostic factors with respect to OS and DFS are shown in **Table 2**. Univariate analysis predicted worse OS and DFS when (1) patients have positive results of pathological examination after ELND ($P = .01$ and $P = .03$, respectively); (2) at least 5.0 mitoses per square millimeter are found ($P = .03$ and $P = .03$, respectively); and (3) location of the primary melanoma is in the head and neck ($P = .02$ and $P = .02$, respectively). The histological characteristics of the primary melanoma, the presence of ulceration, and the sex of the patients were not predictive of long-term outcome. By multivariate analysis (**Table 3**), status of the lymph nodes was most predictive of OS ($P = .003$) and DFS ($P = .009$). The median OS for patients with node-negative and node-positive disease (**Figure 2**) was 209 (5-year survival, 61%) and 49 (5-year survival, 35%) months, respectively. For DFS, these figures were 165 (5-year survival, 56%) and 32 months (5-year survival, 35%), respectively. After multivariate analysis, the location of the primary tumor was a significant prognostic variable for OS ($P = .048$), but not for DFS ($P = .14$). Other prognostic factors did not influence the outcome after multivariate analysis.

COMMENT

The mean OS and DFS in our series were 70 and 51 months, respectively. Univariate analysis of the prognostic variables in our cohort of patients demonstrated sig-

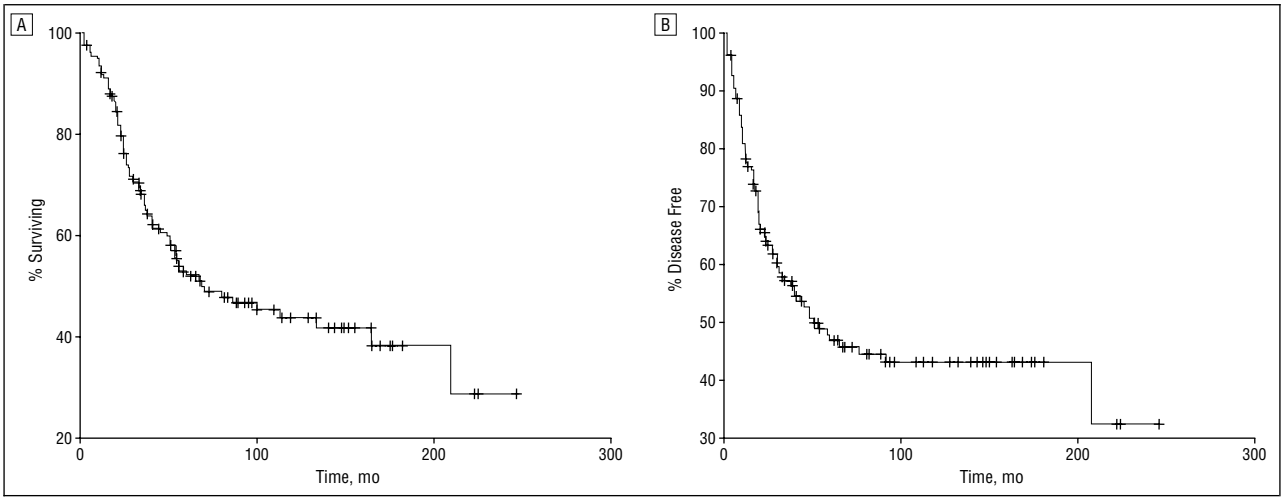

Figure 1. Overall (A) and disease-free (B) survival in the entire population. Median follow-up was 44 months.

Table 2. Univariate Analysis of Overall and Disease-free Survival*

Prognostic Factor	OS	DFS
Nodal status		
Negative	209	165
Positive	49	32
P value	.01	.03
Location of primary tumor		
Lower extremity	113	43
Trunk	100	92
Head and neck	36	25
Upper extremity	149	NR
Perineum	†	†
P value	.02	.02
Mitosis per square millimeter		
<5	165	NR
≥5	56	40
P value	.03	.03
Histological features of primary tumor		
Nodular	60	49
Superficial spreading	113	92
Acral lentiginous	25	18
Lentigo maligna	†	†
P value	.16	.09
Ulceration		
Absent	209	86
Present	56	42
P value	.19	.18
Sex		
Male	54	46
Female	209	149
P value	.14	.17

*Unless otherwise indicated, data are given as number of months. OS indicates overall survival; DFS, disease-free survival; and NR, not reached.
†Indicates all censored or numbers were too small for survival estimates to be completed.

Table 3. Multivariate Cox Regression Analysis of All Prognostic Variables*

	P Value	
Prognostic Factor	OS	DFS
Nodal status	.003	.009
Location of primary tumor	.048	.14
Mitoses per square millimeter†	.11	.13
Histology of primary	.18	.11
Age†	.14	.22
Thickness†	.26	.21
Ulceration	.81	.91
Sex	.58	.66

*Abbreviations are given in the first footnote to Table 2.
†Analyzed as a continuous variable.

nificantly worse survival in patients with node-positive disease, in whom primary melanoma was in the head and neck and in whom melanoma had at least 5.0 mitoses per square miullimeter. Multivariate analysis showed lymph node status to be most predictive of survival. These findings are similar to those of a previous report[4] that reviewed 139 patients with melanoma at least 3.0 mm thick and showed that the pathological stage was most predictive of survival.

The validity of the current results is based on the following: (1) all of these consecutive patients were treated by us; (2) the primary melanoma thickness and other phenotype characteristics were evaluated by one of us (S.G.R.); and (3) for the 121 patients who underwent ELND at the time of initial treatment, the nodal status was known at the time of primary treatment. Furthermore, the surgical technique used in this series was uniform, so although this is a retrospective study, the data generated are valid and can be used to ascertain whether any adjuvant therapy in this subset of patients can be justified.

Kim and colleagues[5] reviewed 120 patients undergoing wide excision with or without regional lymphadenectomy for thick melanoma at Memorial Sloan-Kettering Cancer Center, New York, NY, from 1986 through 1995. Their study was not confined to clinical node-negative disease, and a small percentage of their patients (16%) received adjuvant therapy. Primary tumor ulceration was the most significant predictor of disease-associated mortality in their analysis. Increasing thickness and nodal status at presentation were further predictors of disease relapse and disease-specific mortality.

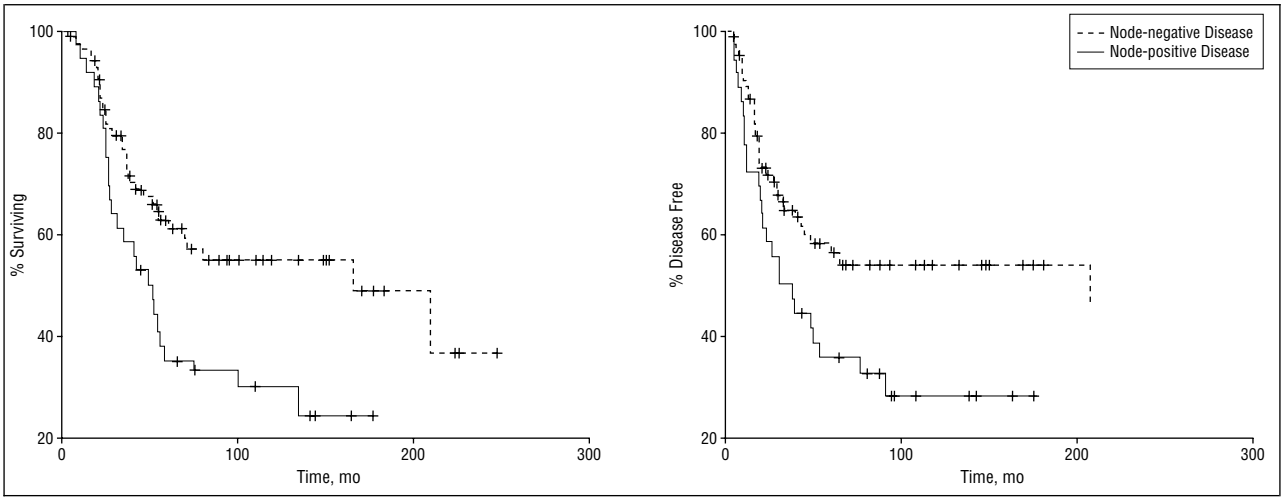

Figure 2. Impact of nodal status on overall (A) and disease-free (B) survival. Patients with lymph node metastases (node-positive disease) had a significantly worse survival than those without lymph node metastases (node-negative disease).

In another retrospective review of 278 patients from the University of Texas M. D. Anderson Cancer Center, Houston, and the H. Lee Moffitt Cancer Center, Tampa, Fla, with a median follow-up of 27 months, nodal status, thickness, and ulceration were significantly associated with overall survival.[6] However, that review included 23 patients (8.3%) who had clinically evident nodal disease and were not excluded from the statistical analyses. Thus, comparisons cannot be made between our results and theirs. However, long-term survival in patients with thick melanomas is not universally poor. Rather, lymph node status is the most important prognostic factor. These findings have been confirmed by at least 2 studies showing that the status of the sentinel node in patients with thick melanomas is the most significant prognostic factor.[7,8] Curiously, in our study, when stratified according to the presence or absence of ulceration in the primary tumor, ulceration was not a significant prognostic marker. In a previous study,[9] we found ulceration to be of prognostic significance in patients whose melanomas were 2 to 4 mm thick.

Our data suggest that patients with thick melanoma (T4 N0 M0) are expected to have favorable survival with aggressive surgery alone when disease has not spread to the regional lymph nodes. Furthermore, randomized trials have failed to show a definite survival benefit of adjuvant therapy in this subset of patients with melanoma. The pivotal Eastern Cooperative Oncology Group Trial E1684 demonstrated that adjuvant therapy with high-dose interferon alfa-2b vs observation significantly prolonged DFS (37% vs 26%) and OS (46% vs 37%).[10] Thus, adjuvant treatment with high-dose interferon alfa-2b was approved for high-risk melanoma by the US Food and Drug Administration in 1995. Although the authors conceded that the number of patients with thick melanoma without concomitant regional node metastases was small, they still recommended that all such patients be treated with adjuvant interferon alfa-2b irrespective of the pathological status of the regional nodes (although no impact of therapy was reported). Two other randomized studies[11,12] have recently been published in which patients with thick melanomas were included in the analyses. The intergroup trial E1694/S9512/C509801[11] was designed to evaluate high-dose interferon alfa-2b vs GM2-KLH/QS-21 vaccine in patients with resected stages IIB to III melanoma. Adjuvant treatment with interferon alfa-2b was recommended for all high-risk patients, including those with T4 N0 melanomas. However, more than two thirds of the patients with clinical T4 N0 disease did not undergo surgical staging, making comparisons between patients with node-negative and node-positive disease difficult. Similarly, the intergroup trial E1690/S9111/C9190 comparing high- and low-dose interferon alfa-2b in patients with high-risk melanoma demonstrated a relapse-free survival benefit in patients receiving high-dose interferon alfa-2b.[12] This study included 163 patients with thick melanomas. However, the nodal status was known by means of results of ELND or sentinel node biopsy in only 27% of patients. Therefore, we believe that the thickness of melanoma, by itself, should not be used as a criterion for adjuvant therapy unless as part of a clinical study. These patients should first receive aggressive locoregional treatment, which should include wide excision and a sentinel lymph node biopsy. If the results of the sentinel node biopsy demonstrate evidence of nodal metastases, complete node dissection is recommended.

Similarly, Gershenwald et al[8] evaluated survival in patients with thick melanomas and found statistically significant differences between patients with sentinel node-negative and sentinel node-positive disease in 3-year DFS (82.4% vs 58%, respectively) and OS (89.4% vs 58%, respectively). They also concluded that patients with sentinel node-negative disease may be either followed up by with observation or enrolled in adjuvant therapy trials.

A previous review of our patients showed that a properly performed LND results in excellent regional control.[13] Attention can then be turned to preventing metastatic disease and improving OS. Patients with nodal metastases are candidates for adjuvant therapy. Those without nodal disease constitute a favorable patient group and thus have much better prognosis and may not need adjuvant therapy. However, they must be closely monitored or enrolled in randomized trials.

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