

Melanoma in the Elderly Patient

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Background: The incidence of cutaneous melanoma is rising steadily, and the rate of increase is among the highest for any form of cancer. Although the reliability of age as a prognostic factor is debatable, several studies suggest that age has an important prognostic use.

Hypothesis: Age alone does not predict a poor prognosis in the older patient with melanoma.

Setting: University teaching hospital.

Methods: A retrospective review was undertaken to identify patients aged 65 years or older with intermediate-thickness melanoma (1-4 mm). Two hundred thirteen such patients were identified. Data are given as mean \pm SD.

Results: The mean age was 72.2 ± 6.1 years. The mean follow-up was 49 months. By univariate analysis, the mean disease-free survival (DFS) and overall survival (OS) for lymph node–positive patients was 36.0 ± 9.6 and 56.0 ± 10.6 months, respectively. The mean DFS for node-negative patients was 155.0 ± 9.8 months, and the mean OS was

166.0 ± 9.2 months ($P < .001$ for both). The mean DFS and OS for women were 151.0 ± 11.2 and 163.0 ± 10.9 months, respectively. In contrast, men had 116.0 ± 9.5 months' DFS and 127.0 ± 9.0 months' OS ($P = .01$ for both). By multivariate analysis, lymph node status was the most predictive variable for DFS and OS ($P < .001$ for both). Sex tended to affect OS ($P = .02$) but did not achieve prognostic significance on DFS ($P = .09$). Other factors such as location, ulceration, histological type, and mitoses per square millimeter failed to show any prognostic significance. Stratification into 3 age groups (65-70, 71-80, and >80 years) had no significant effect on DFS ($P = .95$) or OS ($P = .92$).

Conclusions: Lymph node status is the most important prognostic factor in older patients with intermediate-thickness melanoma. Identification of high-risk factors may help stratify these patients for recommendation of more aggressive treatment or adjuvant therapies. Among these patients, age alone was not a significant prognostic factor in the clinical management of melanoma.

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THE INCIDENCE of cutaneous melanoma is rising steadily, and the rate of increase is among the highest for any form of cancer.^{1,2} Although the incidence of melanoma in younger populations appears to be leveling off or decreasing, the rate continues to rise in older persons.^{3,4} As the geriatric population increases in the United States, melanoma will be an important public health issue in this century.

Many prognostic factors have been studied for cutaneous melanoma: thickness, ulceration, clinical stage, anatomical site, mitoses per square millimeter, sex, and age. Although the reliability of age as a prognostic factor is debatable, several studies⁴⁻⁷ suggest that age has an important prognostic use. Our objective was to determine the role of age as a prognostic factor in intermediate-thickness melanoma.

METHODS

We identified 213 patients aged 65 years or older with intermediate-thickness melanoma

(1-4 mm) in the registry of the Department of Surgical Oncology from May 12, 1961, to October 29, 1998. All patients had received surgical treatment from the department's faculty and it consisted of surgical wide excision of the primary lesion. Complete regional lymph node dissection (LND) was performed simultaneously in 128 of the 213 patients.

Data on the 213 patients were analyzed to evaluate known prognostic variables such as age, sex, histological characteristics, location of primary tumor, number of mitoses per square millimeter, and ulceration relative to disease-free survival (DFS) and overall survival (OS). We also analyzed the effect of nodal status on DFS and OS in the 128 patients who underwent LND. We evaluated the prognostic variables using the Kaplan-Meier method, with log-rank comparison. Multivariate analyses were done using Cox regression analysis. Differences were significant at $P < .05$. Analyses were performed using SPSS software, version 10.1 (SPSS Inc, Chicago, Ill). Death due to melanoma was considered the only event for OS. Disease-free survival events included regional recurrences and distant metastases. Data are expressed as mean \pm SD unless otherwise indicated.

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RESULTS

PATIENT CHARACTERISTICS

Two hundred thirteen patients (129 men [60.6%]; 80 women [39.4%]) underwent surgical treatment for intermediate-thickness melanoma (1-4 mm) during the study. Their ages ranged from 65 to 95 years (mean age, 72.2±6.1 years). Of these 213 patients, 128 underwent LND.

TUMOR CHARACTERISTICS

Primary tumor location was in the lower extremity in 67 (31.5%), trunk in 57 (26.8%), head and neck in 49 (23.0%), and upper extremity in 40 (18.8%) (**Table 1**). The most common histological finding was superficial spreading mela-

noma in 100 patients (46.9%). Seventy-seven patients (36.2%) had nodular melanoma, 23 (10.8%) had acral lentiginous melanoma, and 11 (5.2%) had lentigo maligna melanoma. Melanoma was ulcerated in 65 patients (30.5%). We identified 88 patients (41.3%) with 5 or more mitoses per square millimeter.

Of the 128 patients who underwent elective LND, 36 (28.1%) had node-positive disease. Table 1 summarizes the patient and tumor characteristics.

SURVIVAL

Mean follow-up was 49 months. Mean DFS and OS for the entire population were 142 and 146 months, respectively (**Figure 1**). Results of univariate analyses of several prognostic factors with respect to DFS and OS are given in **Table 2**. Univariate analysis predicted worse DFS and OS when patients had positive results of pathological examination after LND ($P<.001$ for both) and when the patient was male ($P=.01$ for both). Mean DFS and OS for node-positive patients were 36.0±9.6 and 56.0±10.6 months, respectively. Mean DFS and OS for node-negative patients were 155.0±9.8 and 166.0±9.2 months, respectively ($P<.001$ for both). Mean DFS and OS for women were 151.0±11.2 and 163.0±10.9 months, respectively. In contrast, men had 116.0±9.5 months and 127.0±9.0 months of DFS and OS, respectively ($P=.01$ for both). Other factors such as location, ulceration, histological type, and mitoses per square millimeter failed to show any prognostic significance. Stratification into 3 age groups (65-70, 71-80, and >80 years) demonstrated no significant effect on DFS ($P=.95$) or OS ($P=.92$) (**Figure 2**).

By multivariate analysis (**Table 3** and **Figure 3**), lymph node status was the most predictive variable for DFS and OS ($P<.001$ for both). Sex significantly affected OS ($P=.02$) but did not achieve prognostic significance on DFS ($P=.09$). After multivariate analysis, other prognostic factors did not demonstrate significance relative to the outcomes.

| | |
|--|------------|
| Sex | |
| Male | 129 (60.6) |
| Female | 84 (39.4) |
| Age, y | |
| Mean ± SD | 72.2 ± 6.1 |
| Range | 65-95 |
| Location of primary tumor | |
| Lower extremity | 67 (31.5) |
| Trunk | 57 (26.8) |
| Head and neck | 49 (23.0) |
| Upper extremity | 40 (18.8) |
| Histological features of primary tumor | |
| Superficial spreading | 100 (46.9) |
| Nodular | 77 (36.2) |
| Acral lentiginous | 23 (10.8) |
| Lentigo maligna | 11 (5.2) |
| Ulceration | |
| Present | 65 (30.5) |
| Absent | 148 (69.5) |
| Mitoses per square millimeter | |
| <5 | 125 (58.7) |
| ≥5 | 88 (41.3) |
| Nodal status† | |
| Positive | 36 (28.1) |
| Negative | 92 (71.9) |

*Data are given as number (percentage) unless otherwise indicated.
†One hundred twenty-eight patients underwent lymph node dissection.

COMMENT

Older patients comprise an important group among those with melanoma. The incidence in the geriatric popula-

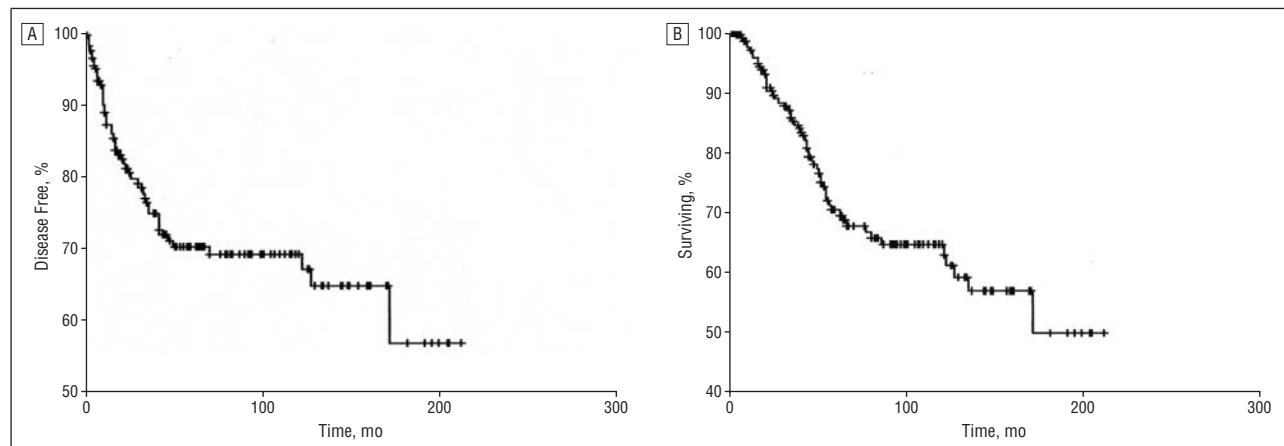


Figure 1. Disease-free (A) and overall (B) survival in the entire population. The mean follow-up was 49 months.

Table 2. Univariate Analysis of Disease-Free and Overall Survival

| Prognostic Factor | P Value | |
|--|-----------------------|------------------|
| | Disease-Free Survival | Overall Survival |
| Nodal status | <.001 | <.001 |
| Location of primary tumor | .46 | .39 |
| Mitoses per square millimeter | .21 | .09 |
| Histological features of primary tumor | .18 | .12 |
| Ulceration | .39 | .33 |
| Sex | .01 | .01 |
| Age stratification | .95 | .92 |

Table 3. Multivariate Cox Regression Analysis of All Prognostic Variables

| Prognostic Factor | P Value | |
|--|-----------------------|------------------|
| | Disease-Free Survival | Overall Survival |
| Nodal status | <.001 | <.001 |
| Age stratification | .93 | .95 |
| Sex | .09 | .02 |
| Location of primary tumor | .62 | .57 |
| Histological features of primary tumor | .31 | .37 |
| Ulceration | .51 | .55 |
| Mitoses per square millimeter | .39 | .36 |

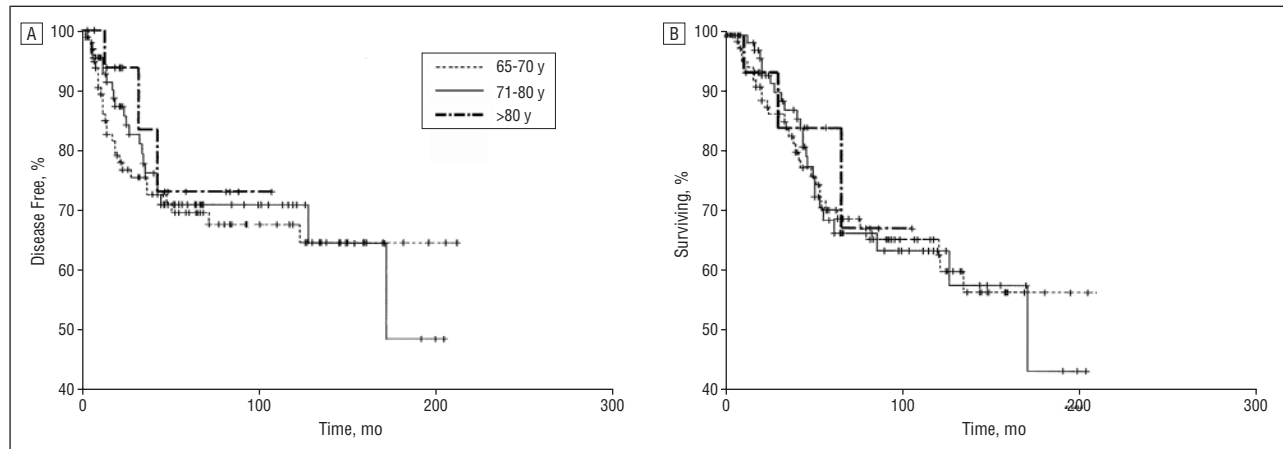


Figure 2. Stratification into 3 age groups (65-70, 71-80, and >80 years) relative to disease-free (A) and overall (B) survival demonstrated no significant effect on survival.

tion continues to rise, although the incidence in the younger populations appears to be leveling off or decreasing.^{2,3} Nearly 50% of all melanoma deaths in the United States are in white men older than 50 years.⁸ Similarly, 50% of deaths from melanoma in New South Wales, Australia, occur in males older than 50, although this age group only accounts for 12% to 14% of the population.⁹

The mean DFS and OS for all patients in our series were 142 and 146 months, respectively. Univariate analysis of the prognostic variables in our cohort of patients demonstrated significantly worse survival in patients with node-positive disease. Multivariate analysis showed lymph node status to be most predictive of survival. Our data suggest that older patients with intermediate-thickness melanoma may have favorable survival with aggressive surgery alone when disease has not spread to the regional lymph nodes.

In our study, women had an increase in OS that did not achieve prognostic significance on DFS. Whether this increase in OS is due to a hormonal factor or an increased life expectancy for women in the United States is hard to substantiate. In addition, we did not evaluate the effect of use of exogenous estrogen on DFS or OS. In comparison, O'Doherty et al¹⁰ reported that older men had a poorer prognosis than older women, but this difference could relate to a lower cutoff age used in their study. The potential sex

difference in prognostic outcome may likely be due to differences in physiological levels of sex hormones. However, there is no clear evidence that hormonal factors have a protective role in melanoma.

Stratification of the sample into 3 age groups (65-70, 71-80, and >80 years) revealed that the DFS and OS were similar among the groups (Figure 3). Simply stated, an 80-year-old patient has the same survival as a 65-year-old patient with the same stage of melanoma. Consequently, our data suggest that age alone should not be used as the exclusion criterion for aggressive surgery in the properly selected patient.

One of the reasons cited for the increased mortality among older patients with melanoma is immunosenescence. As we age, the immune system declines in function, resulting in a decreased capacity to fight infection and malignancy.¹¹ Older persons may have reduced numbers and altered function of Langerhans cells, thus leading to a compromised immune system.¹² Another reason cited for the higher mortality in older persons is the increased thickness of melanoma at diagnosis. Levine et al¹³ hypothesize that decreased skin thickness in older persons permits a deeper level of invasion for lesions of similar thickness. However, this hypothesis is not supported by findings of Loggie et al,⁶ who were not able to correlate increased level of invasion with a given skin thickness. Whether immunose-

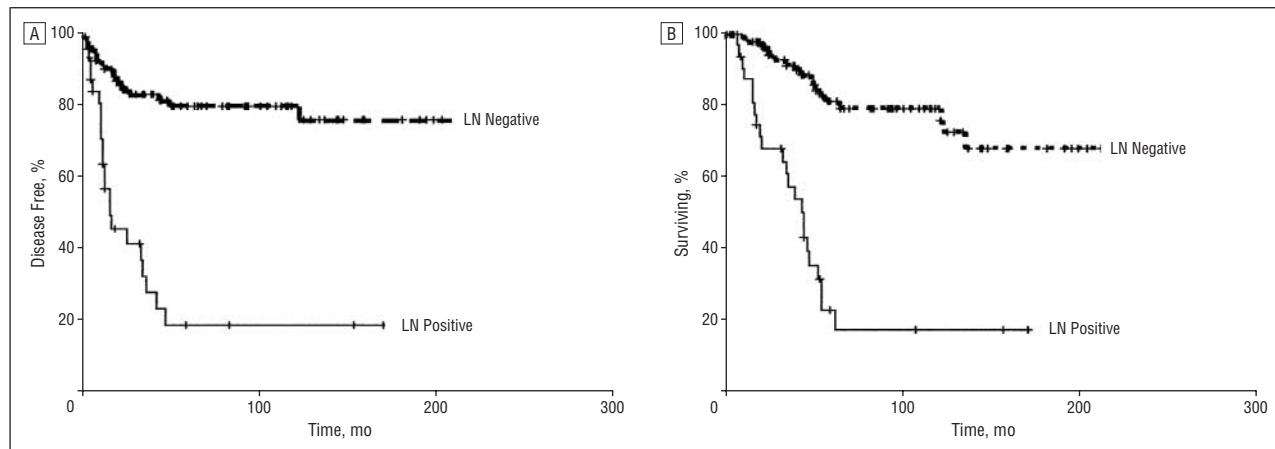


Figure 3. Effect of nodal status on disease-free (A) and overall (B) survival. Patients with lymph node metastases (LN Positive) had a significantly worse survival than those without lymph node metastases (LN Negative).

nescence or skin thickness plays any important role in the OS of older patients with melanoma is uncertain.

Sentinel lymph node (SLN) biopsy has become widely accepted as a method of staging the regional lymph nodes in patients with melanoma. Outpatient biopsy can be performed at the same time as wide local excision of the primary melanoma. It is less morbid than an elective LND and is cost-effective. The advantage of SLN biopsy in melanoma is that it spares 75% to 80% of patients the need for complete regional lymphadenectomy, while identifying those patients at highest risk. The presence of a positive SLN has been shown to be the single most important prognostic factor for recurrence and survival. We perform SLN biopsies on all patients with intermediate-thickness melanoma (1-4 mm). We also perform SLN biopsies on those with melanomas less than 1 mm if they demonstrate ulceration or Clark invasion level IV or V. The usefulness of SLN biopsies on lesions thicker than 4 mm is not clearly defined. In a recent study by Essner et al,¹⁴ the SLN status in thick melanoma was predictive of DFS but not reflective of OS. We routinely perform completion LND if the SLN is found to be positive. The use of this minimally invasive procedure in older populations may help select those who may benefit from completion LND or adjuvant therapy.

Public health initiatives should inform older populations that melanoma is a significant and potentially curable health problem. Marks et al¹⁵ demonstrated the mismatch between the age at which pigmented lesions are excised and older age at which melanoma is likely to occur. Among patients aged 21 to 40 years, the ratio of benign nevus to melanoma among excised lesions was 27.2, compared with 1.4 in those older than 60.¹⁵ Consequently, health care practitioners who work with older persons should increase melanoma screening.

In conclusion, lymph node status is the most important prognostic factor in older patients with intermediate-thickness melanoma. Identification of high-risk factors¹⁶ may help stratify these patients for recommendation of more aggressive treatment or adjuvant therapies. Among these patients, age alone was not a significant prognostic factor in the clinical management of melanoma. Therefore, treat-

ment of patients with melanoma who are 65 years or older should be based on prognostic factors, not advanced age.

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