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Original Research

# Melanoma of the Foot Is Associated With Advanced Disease and Poorer Survival

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ABSTRACT

The purpose of the present study was to review the outcomes and assess the prognostic factors associated with foot melanoma. We hypothesized that primary melanoma of the foot would be more likely to present at an advanced stage and be associated with poorer outcomes. Both univariate and multivariate analyses were conducted to examine the relationships between patients' demographic, clinical, and pathologic characteristics and deaths within 5 years. Categorical data were summarized as frequencies and percentages and continuous variables as mean ± standard deviation. The primary outcome measure was overall survival. On univariate analysis, the significant prognostic variables found included Breslow thickness, ulceration, sentinel node positivity, and localized presentation on the toe. Age, sex, and race were not prognostically significant in this model. Multivariate Cox proportional hazards analysis resulted in a model of foot melanoma with ulceration and location on the toe as independent prognostic variables. The 5-year survival rate for melanoma of the toe was 50%. The results of the present study have shown that physicians should have a low threshold to biopsy suspicious lesions of the foot and ankle. Advanced disease and poorer survival were noted with toe melanoma. An ulcerative lesion of the foot was also associated with poorer survival.



Melanoma has the propensity to mimic ulcerative conditions of the foot and ankle. Compared with neuropathic ulceration secondary to diabetes, alcoholic neuropathy, or trauma, the visual properties of the ulceration might not be distinguishable from invasive melanoma. Often, biopsy of the lesion is required to diagnose invasive melanoma. Awareness of melanoma and the mortality associated with this malignancy is imperative. With early detection, this skin cancer can be treated before the development of advanced disease or deeper lesions.

In the United States, melanoma is the fifth most common cancer among men and the seventh most common cancer among women (1). Although not as common as basal cell and squamous cell carcinoma, melanoma accounts for most skin cancer-related deaths (2). Thickness is one of the most important factors in the prognosis of patients with melanoma (3), and the early diagnosis of thin lesions has been associated with improved outcomes.

Concern exists that primary melanoma of the foot will be associated with a poorer prognosis compared with elsewhere on the body (4). An early diagnosis might be more difficult, because it can mimic other common ulcerative podiatric conditions, can be painless, hidden from the public view, and challenging for even a patient to visualize. Previous studies have suggested that anatomic location on the foot is an independent factor, influencing the survival of patients with melanoma. The 5-year survival rate has been reported to be as low as 52% for patients with melanoma of the foot and ankle compared with 84% for patients with melanoma elsewhere on the lower extremity (5).

The aim of the present study was to review the outcomes and assess the prognostic factors associated with foot melanoma. We hypothesized that primary melanoma of the foot would be more likely to present at an advanced stage and be associated with poorer outcomes.

## Patients and Methods

### *Study Design, Setting, and Patient Selection*

Data for the present retrospective cohort study were obtained from the Kaiser Permanente Northern California (KPNC) database. KPNC is an integrated healthcare delivery system composed of 22 hospitals and 65 clinics serving >3.9 million people in Northern California. The Kaiser Foundation Research Institute's Northern California institutional review board approved the present study.

The demographic, clinical, pathologic, and mortality data were extracted from the KPNC electronic medical records. The initial cohort was identified through the KPNC cancer registry using the International Classification of Diseases, 9th revision, codes.

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We reviewed the medical records to confirm the clinicopathologic factors, including Breslow depth, sentinel lymph node status, presenting location on the foot, ulceration, and tumor stage. All patients aged ≥18 years with a diagnosis of primary melanocytic lesions of the foot from January 2007 through December 2009 were included in the present study. The follow-up interval started from the date of diagnosis and continued to the event (death) or right censoring (date of disenrollment from the health plan or the end of the follow-up [December 31, 2014]), whichever occurred first. A total of 76 patients were included. A spectrum of melanocytic diseases of the foot, ranging from melanoma in situ to metastatic melanoma, were identified. The American Joint Committee on Cancer, 7th edition, was used for staging. The pathologic variables included Breslow thickness, ulceration, and sentinel lymph node involvement. The location on the foot at presentation was documented and classified as dorsal, plantar, toe, rearfoot, and forefoot. The forefoot was divided from the rearfoot by the tarsometatarsal joint complex.

*Statistical Analysis*

Both univariate and multivariate analyses were conducted to examine the relationships between the patients' demographic, clinical, and pathologic characteristics and deaths within 5 years. The clinicopathologic factors studied were chosen according to a previously demonstrated or suspected association with the outcome. Categorical data was summarized as frequencies and percentages and continuous variables as the mean ± standard deviation. The outcome was overall survival. Clinically relevant and statistically significant variables found on univariate analysis were introduced into the multivariate model. The Kaplan-Meier method was used to calculate the survival curves according to the patient characteristics. Log-rank tests were conducted to compare the survival curves stratified by the patient characteristics.

We performed a Cox proportional hazard regression model to estimate the associations between the sociodemographic and clinical characteristics and deaths within 5 years. The exact method was used to handle ties in failure times in the Cox proportional hazard model. We also tested the goodness of fit for the model by creating 10 groups according to the ranked values of the estimated linear predictors and calculating the partial likelihood ratio test to compare the final model to the model with 9 additional variables. Unadjusted and adjusted hazard ratios and the 95% confidence interval are presented. Follow-up started from the date of diagnosis and continued to the event (death) or right censoring (date of disenrollment from the health plan or end of the follow-up period [December 31, 2014]), whichever occurred first. All tests were 2-tailed, and $p < .05$ was considered statistically significant. All data analysis was performed using SAS, version 9.3 (SAS Institute, Cary, NC).

## Results

The clinicopathologic data are summarized in Table 1. The mean age at diagnosis was 61.7 years (range 20 to 94). Of the 76 patients, 45 were female (59.2%) and 31 were male (40.8%). Also, 53 (69.7%) were white, 11 (14.5%) were Hispanic, 9 (11.8%) were Asian, and 2 (2.6%) were African American. Of the 76 lesions, 33 were on the dorsal foot (43.4%), 29 on the plantar foot (38.2%), and 14 on the toes (18.4%). Forefoot and rearfoot lesions were also reviewed.

A review of the pathologic data revealed 19 patients with in situ disease (Table 1) and 57 patients with invasive melanoma. The distribution of the lesions according to invasion and Breslow depth was as follows: in situ in 19 patients (25%), ≤1 mm in 16 patients (21.1%), 1.01 to 2.0 mm in 10 patients (13.2%), 2.01 to 4.0 mm in 17 patients (22.4%), and >4 mm in 14 patients (18.4%). Of the 76 patients, 22 (29.0%) presented with ulcerated lesions.

Thirty-one patients underwent sentinel lymph node biopsy. Patients with melanoma in situ or thickness <1 mm did not undergone lymph node biopsy. Nor was biopsy performed in 10 patients because advanced metastatic disease was confirmed by positron emission tomography. Of the 31 patients undergoing sentinel lymph node staging, 15 (48.4%) had positive sentinel lymph node disease.

Of the 76 patients, 18 died within 5 years, for an overall 5-year survival rate for invasive melanoma of 68.4%. The 5-year survival of those with lesions 2.01 to 4 mm was 61% compared with 98% for those with lesions <2 mm (Fig. A). Of the 76 invasive melanoma lesions, 54.4% were >2-mm thick. The incidence of ulceration at the initial biopsy was 29%. Of the 22 patients with an ulcerative lesion, 14 had died within 5 years (Fig. D). Therefore, the 5-year survival of patients who presented with an ulcerative lesion was 36%. No patients with melanoma in situ presented with an ulcerated lesion.

**Table 1**
Clinicopathologic features of 76 patients with melanoma

| Characteristic | n (%) |
|---|---|
| Age (y) | |
| Mean | 61.7 ± 16.1 |
| Range | 20 to 94 |
| Sex | |
| Male | 31 (40.8) |
| Female | 45 (59.2) |
| Race | |
| White | 53 (69.7) |
| Black | 2 (2.6) |
| Hispanic | 11 (14.5) |
| Asian | 9 (11.8) |
| Other | 1 (1.3) |
| Family history | |
| Yes | 8 (10.5) |
| No | 35 (46.0) |
| Unknown | 33 (43.4) |
| Localization | |
| Toe | 14 (18.4) |
| Dorsal | 33 (43.4) |
| Plantar | 29 (38.2) |
| Localization | |
| Forefoot | 46 (60.5) |
| Rearfoot | 30 (39.5) |
| Type | |
| In situ | 19 (25.0) |
| Invasive | 57 (75.0) |
| Breslow depth (mm; n = 57) | |
| <1 | 16 (21.1) |
| 1.01 to 2 | 10 (13.2) |
| 2.01 to 4 | 17 (22.4) |
| >4 | 14 (18.4) |
| Ulceration | |
| No | 54 (71.0) |
| Yes | 22 (29.0) |
| Sentinel lymph node involvement | |
| No | 16 (51.6) |
| Yes | 15 (48.4) |
| Stage (n = 76) | |
| In situ | 19 (25) |
| I | 21 (27.6) |
| II | 11 (14.5) |
| III | 12 (15.8) |
| IV | 13 (17.1) |

On univariate analysis, significant prognostic variables were found to include Breslow thickness, ulceration, sentinel lymph node positivity, and presentation on the toe (Table 2). Age, sex, and race were not prognostically significant in this model. Multivariate Cox proportional hazards analysis resulted in a model of foot melanoma with ulceration and location on the toe as independent prognostic variables. The 5-year survival rate for those with melanoma of the toe was 50%.

## Discussion

The results from the present study suggest that melanoma of the foot will be associated with comparatively worse outcomes. The 5-year survival of invasive melanoma of the foot was 68.4%, significantly less than the 5-year survival of 91.7% when the entire body is considered (6). Our data suggest that the outcomes are related to more advanced disease on presentation. Only 56.1% of the patients with invasive melanoma of the foot presented with localized disease in our study. In contrast, the Surveillance, Epidemiology, and End Results Program data quantified 84% of melanoma cases as localized (6). The results from the present study suggested a prevalence of deeper primary foot lesions and greater regional disease at diagnosis, with 54.4% of invasive melanoma lesions >2 mm deep and 48.4% of invasive melanoma having positive sentinel lymph node involvement. This