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COMMENT AND CONTROVERSY
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Clinical and histologic characteristics of clinically unsuspected melanomas

Heidi M. Hermes, MD [a], Joya Sahu, MD [b], Laurel R. Schwartz, MD [b], Jason B. Lee, MD [b,*]

[a]*Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD*
[b]*Department of Dermatology and Cutaneous Biology, Jefferson Medical College of Thomas Jefferson University, 833 Chestnut Street, Philadelphia, PA 19107*

Abstract Thin melanomas are recognized and captured by clinicians at an alarming rate, whereas thick melanomas remain underrecognized. Improved recognition of thick melanomas will require further understanding of their clinical and histologic characteristics at various stages of development because emerging data suggest that the thin melanomas being captured today may not represent the forerunners of the thick melanomas. In this retrospective analysis, pathology requisition forms from melanomas diagnosed by histopathology were examined for submitted clinical diagnosis, patient characteristics, melanoma thickness, and biopsy method. Three hundred eighty-five melanomas were identified from 2003 to 2011. Most lesions (71.7%) were clinically suspected to be melanocytic. The mean depth in this group was 0.62mm. Of the unsuspected cases (28.3%), the most common submitted diagnoses were basal cell carcinomas and seborrheic keratoses, consistent with previous reports. The mean depth in the unsuspected group was 1.64mm, and more frequently extended to the deep margin (51.8% *vs* 25.4% of the time). Shave biopsy was the overwhelming preferred method of biopsy (79.5% overall). Compared with thin melanomas, thick melanomas are underrecognized by physicians due to their lack of characteristic morphologic features; consequently, they are more frequently associated with suboptimal biopsies.

Introduction

Despite the dramatic increase in the incidence of thin melanomas around the world in the last several decades, a corresponding anticipated decline in the incidence of thick melanomas and their associated high mortality have not been observed. Emerging data suggest the existence of three heterogeneous forms of melanomas:(1) fast-growing aggressive melanomas minimally associated with sun exposure and melanocytic nevi, (2) slow-growing melanomas associated with intermittent sun exposure and melanocytic nevi, and (3) slow-growing indolent melanomas associated with chronic sun exposure occurring on the head and neck.[1–3] Because much of the increase in the incidence of melanoma can be accounted for by stage I disease that has a 5-year survival rate approaching 97%,[4,5] the current public and physician efforts appear to have resulted in capturing the thin, slow-growing melanomas (types II and III), but not the thick, fast-growing ones (type I).[6,7] Due to their lack of impact on melanoma mortality, the ever-increasing in situ and thin melanomas being diagnosed today have been described as histologically malignant but biologically benign, inert, or indolent.[8–10] For

* Corresponding author. Thomas Jefferson University Hospital, 833 Chestnut Street, Suite 740, Philadelphia, PA 19107.
E-mail address: jason.lee@jefferson.edu (J.B. Lee).

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some, length bias and overdiagnosis, contributed by increases in scrutiny, biopsy rates, and cancer registration,[9–13] provide the explanations for the current incidence and mortality trends.[9–13] Diagnostic drift, that is, labeling lesions as malignant that previously would have been labeled as benign, has been argued as a significant reason for the overdiagnosis.[14–17] The stable incidence of thick melanomas in the face of capturing thin melanomas on a large scale suggests that the thin and thick melanomas captured today may represent different forms of melanomas rather than the former representing the forerunners of the latter.[1,7,18] Currently, thin melanomas are highly recognized and captured at an ever-increasing rate, whereas thick melanomas with poor prognosis are underrecognized. For thick melanomas, in part due to their rarity, epidemiologic data and clinical characteristics have not been well established and extensively described. Improved recognition of thick melanomas will require further understanding of their clinical and histologic characteristics at various stages of their development; moreover, whether thick melanomas are indeed underrecognized needs further confirmation. In this retrospective analysis of histologically confirmed melanomas, clinically unsuspected and suspected cases are compared with respect to their clinical characteristics, biopsy techniques, and depths.

Materials and methods

After receiving the approval of the investigational protocol by the Thomas Jefferson University Institutional Review Board (Philadelphia, PA), we performed a search of the Jefferson Dermatopathology Center database to identify all cases diagnosed histologically as melanoma during the period of 2003 through 2011. Melanoma insitu was specifically excluded.

The requisition form and report for each melanoma were reviewed to obtain and tabulate age and sex of the patient, sites, clinical diagnosis, biopsy method, margin information, and Breslow's depth. Cases were divided into two groups for analysis based on whether a melanocytic lesion was suspected in the submitted clinical differential diagnosis. If a melanocytic lesion was mentioned on the requisition form, such as atypical, dysplastic, or Clark nevus, lentigo; lentigo maligna; or melanoma, the case was categorized into the *suspected group*, whereas those cases with no mention of a melanocytic lesion were categorized into the *unsuspected group*. Statistical analysis was performed using GraphPad online software (La Jolla, CA). *t*test was used to analyze continuous variables among groups; Fisher exact test was used to analyze categorical variables.

Results

The retrospective review identified 391 cases of melanomas, 6 cases of which were excluded, because no diagnosis was provided on the requisition form, leaving 385 cases for analysis. Dermatologists referred all cases included in the study. Of the 385 cases that were included in the study, 240 were men and 144 were women, whereas the patient's sex was not reported in 1 case. Overall age at diagnosis ranged from 21 to 95 years, with the average being 67 years. The suspected group was composed of 276 cases (71.7%), whereas 109 cases (28.3%) comprised the unsuspected group. The mean age of the suspected and unsuspected groups was 65 and 71 years, respectively. The age difference of the two groups was statistically significant ($p<0.001$), with the unsuspected group being older. There was no difference in the sex distribution between the two groups. Table 1 summarizes patient characteristics.

Table 1 Patient characteristics

	All Cases	Suspected Group	Unsuspected Group
Age (range), y	67 (21-95)	65 (21-87)	71 (43-97)
Sex, *n*			
Men	242	166	74
Women	148	109	35
Not reported, n	1	1	0

Figure 1 demonstrates the clinical diagnoses as submitted by the clinician on the requisition form. In the majority of cases, one diagnosis per specimen was submitted. There were cases, however, where two to four diagnoses were submitted (Table 2). Melanoma appeared on the differential 22% of the cases overall. Basal cell carcinoma was the second most frequent entity on the requisition form (16%). See legend for Figure 1 for list of all diagnoses submitted.

In the suspected group, melanoma was the most commonly mentioned diagnosis (30.4%), followed by atypical, dysplastic, or Clark nevus (20.6%), and followed by melanoma in situ or lentigo maligna (13%), nevus not otherwise specified (10%), and lentigo (7%). Spitz nevus accounted for only two cases (0.5%). Other diagnoses commonly included on the differential in this group were seborrheic keratosis (7%) and basal cell carcinoma (6%).

In the unsuspected group, basal cell carcinoma was mentioned most frequently (42.6%), followed by seborrheic keratosis (19.9%) and squamouscell carcinoma (15.6%). Interestingly, neoplasm not otherwise specified was more frequent in this group (6.4%). By definition, no melanocytic lesions were included on the differential in this group.

The depths of the melanomas ranged from 0.1 to 12 mm, and the mean depth was 0.90 mm for all melanomas. The mean depth of the suspected group was 0.62 mm, whereas the mean depth in the unsuspected group was 1.64 mm. This difference was statistically significant ($p<0.001$), indicating that the unsuspected group had a greater depth at initial biopsy. Extension to the base of biopsy was found to be 25.4% in the suspected group compared with 51.8% in the unsuspected group, which is also statistically significant ($p<0.001$). Extension to the peripheral margin was more