Greater distance to an academic medical center is associated with poorer melanoma prognostic factors: The University of Colorado Experience

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Abstract

Introduction: Numerous studies report a correlation between distance to diagnostic provider in an academic medical center and poorer prognosis of disease. Limited research on this topic exists with respect to melanoma.

Methods: This was a retrospective chart review of 1,463 adults (≥18 years) initially diagnosed with melanoma between 2006-2016. Associations between distance traveled and Breslow depth and presence of metastatic disease were assessed via cumulative and binary logistic regression models, adjusting for patient and tumor characteristics.

Results: Subjects traveling ≥50 miles had 58% greater odds of having an increased Breslow depth than those traveling less than that distance (OR: 1.58; 95% CI: 1.24-2.01; p<0.0001), and had four times the odds of presenting with metastatic disease (OR: 4.04; 95% CI: 3.00-5.46; p<0.0001).

Discussion: We highlight the correlation between increased distance to our academic medical center with greater Breslow depths and the presence of metastatic disease at presentation.

Conclusion: Future studies assessing other factors and regional differences that limit access to diagnosis might help improve screening efforts to prevent poorer prognosis for patients in these areas.

Keywords: Breslow depth, malignant melanoma, metastatic melanoma, melanoma

Introduction

The incidence of malignant melanoma (MM) has steadily risen over the past decade [1, 2]. Numerous studies have identified tumor prognostic factors including Breslow depth, ulceration, level of invasion [3, 4], cell type, and mitotic rate [5]. Of these factors, Breslow depth of invasion has the highest prognostic significance [6, 7]. The presence of metastatic disease further denotes particularly poor prognosis with 5-years survival rates reported between 5-19% [6].

Early identification of lesions allows for the diagnosis of tumors with smaller Breslow depths and better outcomes. Patients with suspicious lesions must undergo clinical examination and the diagnosis ultimately depends on biopsy results [7, 8]. Although some primary care physicians perform diagnostic biopsies, they often refer their patients to dermatologists or surgeons, delaying access to care [9].

Numerous studies have identified links between travel distance to health care and poor outcomes of various cancers [10-13]. Increased travel distance to care often delays appropriate screening, early detection, and prompt treatment [9]. Sociodemographic factors such as rural location, low income, and low education may further decrease adequate access to health care

Table 1: Patient Demographics

Table 1: Patient Demographics; N (%).					
Location	Not Urban	384 (33.28)	***State***	Colorado	1049 (90.74)
	Urban	772 (66.72)		Other	107 (9.26)
			Miles Traveled to Center		
		< 12.5	**12.5-49.99**	**50-249.99**	**≥250**
***Age* (years)**	18-29	13 (23.21)	23 (41.07)	14 (25.00)	6 (10.71)
	30-39	19 (13.38)	72 (50.70)	43 (30.28)	8 (5.63)
	40-49	29 (16.96)	90 (52.63)	42 (24.56)	10 (5.85)
	50-59	31 (11.57)	135 (50.37)	80 (29.85)	22 (8.21)
	60-69	34 (12.19)	133 (47.67)	91 (32.62)	21 (7.53)
	70-84	29 (14.22)	90 (44.12)	70 (34.31)	15 (7.35)
	85+	7 (19.44)	19 (52.78)	6 (16.67)	4 (11.11)
All Subjects	18-85+	162 (14.00)	562 (48.60)	346 (29.90)	86 (7.40)
Gender	Male	91 (13.98)	315 (48.39)	195 (29.95)	50 (7.68)
	Female	71 (14.06)	247 (48.91)	151 (29.90)	36 (7.13)
Family History	Yes	31 (15.05)	99 (48.06)	61 (29.61)	15 (7.28)
	No	131 (13.79)	463 (48.74)	285 (30.00)	71 (7.47)
Relationship Status	Divorced	4 (14.29)	14 (50.00)	8 (28.57)	2 (7.14)
	Married/ Significant other	98 (13.07)	352 (46.93)	241 (32.13)	59 (7.87)
	Single	51 (16.67)	160 (52.29)	79 (25.82)	16 (5.23)
	Widowed	1 (5.56)	7 (38.89)	6 (33.33)	4 (22.22)

Table 1. *Patient demographics for a total of 1,156 subjects. No significant difference was observed between age, gender, relationship status, family history of melanoma and miles traveled to academic medical center.*

[14-16].

Specific to MM, a 2007 study of 643 patients in 42 North Carolina counties revealed a positive but weak correlation between Breslow depth and distance to diagnostic provider. Although this study identified a significant relationship, investigations have not occurred in recent years, despite technological advancements in diagnostic tools for MM [17]. Furthermore, limited research on this relationship in the Western U.S. exists.

Methods

General Study Design: This was an Institutional-Review Board (IRB)-approved retrospective chart review of adults (≥18 years) initially diagnosed with MM between 2006-2016. Demographic information and clinical tumor information were extracted from electronic medical records. Distance to the academic medical center was calculated using patient zip codes in Google Maps. Relationships were analyzed using statistical software.

Setting: Data was collected at the University of Colorado Anschutz Medical Campus by research personnel between March 2016-November 2016.

Participants: A list of medical record numbers (MRNs) of adults initially diagnosed with melanoma between January 2006 (when the Electronic Medical Record [EMR] became widely used) and March 2016 was generated from two sources: 1) Dermatology Flow Sheets in the EMRs from our outpatient dermatology clinic and 2) the melanoma data bank of the cutaneous oncology clinic. Dermatology flow sheets are completed for all patients seen in our outpatient dermatology clinic upon diagnosis of MM. All patients with MM in the cutaneous oncology clinic are entered into the melanoma data bank as per departmental protocol. EMRs of all subjects were then obtained using their MRNs. Subjects without reportable Breslow depths, including those with melanomas in situ, ocular melanoma, and unidentifiable primary lesions were excluded from analyses.

Variables: Demographic data extracted from EMRs included: sex, age, ethnicity, relationship status, and family history of melanoma. Geographic region of residence (rural, urban) was coded using the 2010 Urban Census Urban and Rural Classification [19]. Distance to treatment facility (in miles) was calculated using the patient's residential zip code in Google Maps (© 2015 Google Inc, used with permission. Google and the Google logo are registered trademarks of Google Inc.). Clinical data extracted from the pathology reports in the EMR included: Breslow depth, histological melanoma type, body side, anatomic location, ulceration, and tumor mitotic rate.

Bias: The potential for reporting bias existed, as the information regarding the diagnosis of melanoma was obtained via chart review. This bias was minimized with the use of the EMR, which made data highly accessible and attainable.

Statistical methods: Descriptive statistics were generated to describe patient characteristics. Breslow depth was categorized into three a priori categories (<1.0, 1.0-4.0, > 4.0). Distance traveled was categorized into four a priori categories (<12.5 miles, <50 miles, <250 miles, ≥ 250 miles). The association between categorized Breslow depth and miles traveled was assessed via Stuart's Tau C statistic. The association between metastatic disease and Breslow depth category was assessed via Cochran-Armitage test. A multivariable cumulative logistic regression model for Breslow depth category and logistic regression model for metastatic disease were estimated to examine the relationship between distance traveled adjusting for patient and tumor characteristics. Estimated odds ratios and 95% confidence intervals from these models are presented. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC) and two-sided p-values less than 0.05 were considered statistically significant.

Table 2: Distance Traveled to Medical Center vs. Breslow's Depth and Presence of Metastatic Disease; N (%)

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		Miles Traveled to Center				
		< 12.5	12.5-49.99	50-249.99	≥250	Total
Breslow's Depth [A]	< 1.0 mm	74 (45.7)	225 (40.0)	95 (27.5)	23 (26.7)	417
	1.01-4.0 mm	63 (38.9)	279 (49.6)	189 (54.6)	51 (59.3)	582
	> 4.0 mm	25 (15.4)	58 (10.3)	62 (17.9)	12 (13.9)	157
Metastatic Disease [B]	Yes	15 (9.26)	107 (19.04)	154 (44.51)	36 (41.86)	312

[A] Stuart's Tau-C statistic (95% CI) and p-value for association: 0.11 (0.06,0.16) p-value < 0.001

[B] Cochran-Armitage p-values for trend: < 0.001 (metastatic disease)

Table 2. *Breslow's depth & metastatic disease presence vs. miles traveled. Subjects traveling ≥50 miles had a significant association with increased Breslow's depth between 1.01-4.00 mm as compared to those traveling ≤49.99 miles (p<0.001). Presence of metastases at initial diagnosis was also found disproportionally in subjects traveling farther (p<0.001); 86.37% of patients with metastases traveled ≥50 miles.*

Results

Study Population: A total of 1,463 medical record numbers were obtained. Of these cases, 307 (20.9%) subjects without reportable Breslow depths, including those with melanomas in situ (n=101), ocular melanoma (n=40), and unidentifiable primary lesions (n=166) were excluded. We included a total of 1,156 subjects, with 772 (67%) from urban area and 384 (33%) from non-urban areas (**Table 1**). No significant differences existed between age, gender, relationship status, family history of melanoma, and miles traveled to academic medical center.

Distance and Prognostic Factors of Disease: In the overall sample, there was a statistically significant association between greater distance traveled and increased Breslow depth; the proportion of patients with Breslow depth between 1.01-4.00 mm was greater for those traveling ≥50 miles compared to those traveling ≤49.99 miles (p<0.001, **Table 2**).

Those patients who presented with metastases (n=312) were also disproportionally represented at greater distances. Although 9% of subjects traveling <12.5 miles and 19% of subjects traveling between 12.5 and 49.99 miles had metastatic disease at initial diagnosis, a much higher percentage of those traveling 50-249.99 miles and ≥250 miles presented with metastatic disease (45% and 42% respectively, p for trend ≤0.001).

Ulceration displayed a non-significant trend towards patients at a greater distance to diagnosing provider, 41% at ≥250 miles compared to 28%, 26%, and 26% increasing in distance within the other three groups (p-valuel0.16). No significant associations between distance to diagnosing provider and mitotic rate were detected within our cohort.

Our multivariable cumulative logistic regression models also demonstrated similar statistically significant associations. Subjects traveling ≥50 miles to their diagnosing provider had 58% higher odds of having an increased Breslow depth at diagnosis

Table 3: Multivariable Cumulative Logistic Model for Breslow's Depth and Metastatic Disease

	Breslow's Depth				Metastatic Disease			
	Odds Ratio	95% Confidence Limits		p-value	Odds Ratio	95% Confidence Limits		p-value
Distance Traveled: **≥50 miles (Ref: <50 miles)**	1.58	1.24	2.01	<0.001	4.04	3.00	5.46	<0.001
Gender: **Male (Ref: Female)**	1.32	1.04	1.68	0.021	1.72	1.26	2.34	<0.001
Age **(years)**	1.01	1.00	1.02	0.035	1.02	1.01	1.03	<0.001
Melanoma Type: **Acral lentiginous**	1.99	1.04	3.83	0.039	1.29	0.52	3.18	0.277
Lentigo maligna melanoma	0.31	0.15	0.61	<0.001	0.78	0.33	1.85	0.011
Nodular	8.72	6.04	12.57	<0.001	7.93	5.18	12.15	<0.001
Other	7.42	4.43	12.42	<0.001	3.03	1.68	5.49	0.068
Unspecified	2.91	2.19	3.85	<0.001	2.18	1.49	3.18	0.456
(Ref: Superficial spreading								

Table 3. *Breslow's depth and metastatic disease: multivariable cumulative logistic models. Subjects traveling ≥50 miles had 58% greater odds of having an increased Breslow's depth (OR: 1.58; 95% CI: 1.24-2.01; p<0.0001), and had four times the odds of presenting with metastatic disease (OR: 4.04; 95% CI: 3.00-5.46; p<0.0001) as compared to those traveling shorter distances. Significance was retained after adjustments for gender, age, and melanoma subtype.*

than those traveling less than that distance (OR: 1.58; 95% CI: 1.24-2.01; p≤0.0001, **Table 3**). Significance remained after adjustments for age, gender, and melanoma subtype. Consistent with the literature, nodular type melanoma, male gender, and increasing age were also associated with increased Breslow depth (nodular type: OR=8.72; 95% CI: 6.04-12.57 p≤0.0001, male gender: OR=1.32; 95% CI: 1.04-1.68; p=0.02, age: OR=1.01; 95% CI: 1.00-1.02; p=0.03, **Table 3**). Interestingly, the increase in Breslow depth was observed to have plateaued at approximately 150 miles, but it was still greater than the depth at less than 50 miles (Scatterplot, **Figure 1**). This decrease may be a nuance of our data or indicative of proximity to other bordering medical centers.

Even more robust was the association that we saw between presentation with metastatic disease and distance from diagnosing provider. Patients who traveled 50 miles or greater as compared with those traveling shorter distances had four times the odds of presenting with metastatic disease (OR: 4.04; 95% CI: 3.00-5.46; p≤0.0001, **Table 3**). Similar to Breslow depth, nodular type melanoma, male gender, and increasing age were also associated with increased metastatic disease at initial presentation (nodular type: OR=7.93; 95% CI: 5.18-12.15 p≤0.0001, male gender: OR=1.72; 95% CI: 1.26-2.34; p=0.0006, age: OR=1.02; 95% CI: 1.01-1.03; p≤0.0001, **Table 3**).

Discussion

Key results & Interpretation: This study identifies important differences in prognostic factors for those living at greater distances from diagnosing providers including both Breslow depth and metastatic disease at initial presentation. Although the 2007 study by Stitzenberg et al. revealed an association between Breslow depth and distance from diagnosing providers, the study captured a smaller geographical area in which 99% of participants traveled under 120 miles [9]. Our study confirms this relationship on a greater scale and within a different region in the United States. It additionally demonstrates the association between distance to diagnosing provider and metastatic disease upon initial presentation, which is the single most influential factor for tumor,

node, and metastasis staging and subsequently 5-year mortality [19]. Future studies combining distance to health centers along with other barriers to care might help to establish health care models that can predict which patient populations might be at higher risk for MM. In larger metropolis areas where there is often access to more than one medical center, multicenter regional studies could help to clarify this likely more complicated relationship. These studies could possibly identify "watershed areas" within urban centers where patients have disproportionally high rates of poor prognostic factors of disease related to increased distance health centers or decreased accessibility to care through other socioeconomic factors. Such models may guide local and national screening efforts to improve the disproportionally poor prognosis within these groups.

Limitations: Because this was a single center study, distance to this academic medical center is not necessarily representative of distance to any health center. However, this limitation was minimized owing to the fact that University of Colorado is the only academic medical center in the state and there are no large academic medical centers within a 500-mile radius. Overlap with other medical centers may have occurred only at the greatest distances included within our study, over 150 miles (**Figure 1**). The potential for referral bias further existed, as patients may have been referred from either a primary care physician or dermatologist with more advanced disease. To limit this bias, information was only collected on patients with definitive diagnoses obtained via biopsy for Breslow depth at the University of Colorado. Additionally, the concentrated geographic distribution of providers in Colorado within the Denver metropolitan area limits the potential for referral bias. Confounding variables such as education, household income, and health insurance were not included within the analysis, as these variables were not readily accessible within the EMR.

Generalizability: Although this study's generalizability is limited to its single-institution design, the results were consistent with a 2007 North Carolina study [10]. Future nation-wide population based studies may further identify how these relationships hold at the state, regional, and national level.

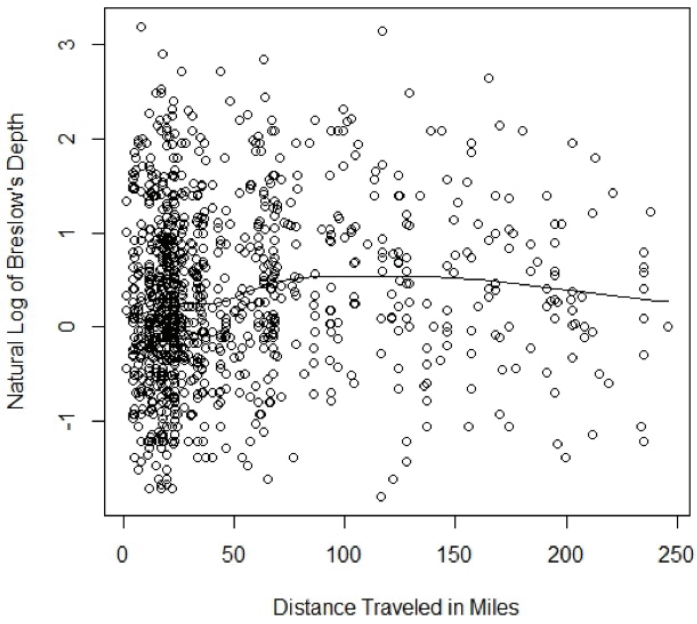

Figure 1. *Scatterplot of Breslow›s depth (log transformed) versus miles traveled. As indicated by the smoothed line, presenting depths tend to be higher at distances over ~50 miles, and flatten out at distances over about ~150 miles. Long distances (>250 miles) were excluded from analyses.*

Conclusion

Our study demonstrates a significant relationship between increased distance to diagnosing physician and some of the more influential poor prognostic factors of malignant melanoma, including metastatic disease at presentation and Breslow depth. Future studies analyzing regional differences might help identify unknown melanoma hot spots, where a higher incidence of MM exists. In turn, this information could help to increase local awareness and local physician screening efforts. Furthermore, such findings may inform national screening programs to help target areas where the establishment and implementation of screening programs can be maximally efficacious.

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