

National Analysis of Patients With Ulcerated Melanoma in the United States

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Abstract. *Background/Aim:* Ulceration is associated with unfavorable prognosis in patients with melanoma. The present study aimed to analyze the characteristics associated with ulcerated melanoma in the United States. It was hypothesized that patient disparities associated with increased odds of ulceration exist. *Patients and Methods:* We searched the National Cancer Database for melanoma patients from 2004 to 2015. Data regarding patient demographics, facility characteristics, and tumor characteristics were analyzed. *Results:* There were higher odds of ulceration in non-white patients, 50 years of age or older, and melanoma on the trunk and extremities. Lower odds were found in women, zip codes with higher income and education levels, and Metro or Urban counties. *Conclusion:* Age above 49 years, male sex, non-white race, living in rural areas, and living in zip codes with low income and low education were independently associated with ulcerated melanoma.

Melanoma incidence in the United States has been rising over the past 50 years (1-3). Increased life expectancy has likely contributed to this statistic, but is not the only responsible factor. Ulceration of melanomas is the result of destruction of the epidermis by the proliferating neoplastic cells and modification of blood supply caused by the expansile activity of the tumor (4). Since ulceration is associated with unfavorable prognosis, it should be

investigated in the clinical history of patients to achieve a careful diagnostic work-up and follow-up (5). Our aim was to analyze the characteristics associated with ulcerated lesions among melanoma patients in the United States. We hypothesized that patient disparities are associated with increased odds of ulceration.

Patients and Methods

This analysis was conducted using the National Cancer Database (NCDB), an initiative driven by the American Cancer Society and the American College of Surgeons' Commission on Cancer that registers 70% of all cancer diagnoses in the United States (6). This study was considered nonregulated by the institutional review board. Data were extracted for all patients diagnosed with melanoma from January 1, 2004, to December 31, 2015. The cohort was then split into 2 groups based on presence of ulceration: (i) ulcerated melanoma or (ii) non-ulcerated melanoma. Patients for whom presence of ulceration was unknown were excluded.

Patient demographics, facility and treatment characteristics, and tumor characteristics were collected. Patient demographics included age, gender, race, income (median household income for patient's zip code), education (percentage of adults who did not graduate from high school in patient's zip code), and insurance status (uninsured, private, Medicaid, Medicare, other government, unknown). Facility and treatment characteristics included facility type. Tumor characteristics included tumor invasive behavior, Breslow depth, American Joint Committee on Cancer (AJCC) stage, and body location.

Patient demographics, facility and treatment characteristics, and tumor characteristics were analyzed using χ^2 or Mann-Whitney tests as appropriate. Multivariate analysis was performed using logistic regression to assess independent associations, adjusting for confounders. The outcome variable was ulceration (1, ulcerated melanoma; 2, non-ulcerated melanoma) and the predicted variables were patient demographic characteristics. The significance level was set at $p < 0.05$. Statistical analysis was performed using SPSS 25.0 statistical software (SPSS Inc.).

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Key Words: Head and neck neoplasms, ulcerated melanoma, NCDB, United States/epidemiology.

Results

A total of 459,211 patients met the criteria of the study. The analyzed cohort included 393,812 (85.8%) patients with non-ulcerated melanoma and 65,399 (14.2%) with ulcerated melanoma. Ulcerated melanoma was significantly more prevalent among men and within patients older than 70 years ($p<0.001$). Patients with private insurance were found to present a significantly lower rate of ulcerated melanoma ($p<0.001$), and patients with ulcerated lesions were found to be treated at Academic/Research programs less frequently compared to patients with non-ulcerated lesions ($p<0.001$) (Table I).

Higher odds of ulceration were found in non-white patients compared to white patients; 50 years of age or older compared to 49 years or younger; and melanoma located on the trunk and extremities compared to head and neck. On the other hand, lower odds of ulceration were found in women compared to men; patients who lived in a zip code with higher income and educational levels; and in metro or urban counties compared to rural (Table II).

Discussion

Ulceration has been described as a predictive tumor characteristic related to melanoma prognosis (7). However, factors associated with ulcerated melanoma are still unexplored. To our knowledge, this is the largest study to date on ulcerated melanoma and the first to provide an analysis of demographic and socioeconomic factors associated with these lesions in a large national cancer database. Interestingly, higher odds of ulceration were observed in patients who were older than 50 years old, men, non-white race, living in rural areas, and living in zip codes with low income and low education.

Previous inquiry has indicated that the presence of ulceration is related to worse survival and lymph node positivity (8, 9). One potential explanation for poor survival rates in malignant melanoma may be the radial and vertical growth characteristics of the tumor, facilitating metastasis (10). Although ulceration of melanoma lesions is identified in a small proportion of the overall population of thin melanoma lesions, it remains an important and substantial prognostic sign to determine appropriate treatment. These additional treatment strategies take into account that ulceration has been associated with worse survival and more aggressive disease, predicated more aggressive management, longitudinal sentinel lymph node evaluation, and adjuvant combination treatment. There are active trials underway in the United States investigating the efficacy of adjuvant therapies, such as immunotherapy, in ulcerated and non-ulcerated melanoma lesions of various AJCC stages (7).

Overall, 14.2% of patients in our study had ulcerated melanoma. A similar frequency was found by Cherobin *et al.*

(11) in a cohort of 514 patients, where 13.6% had ulceration on pathologic examination. The mean age of the patients with ulcerated melanoma identified in our study was 64.75 years, most of them being white men diagnosed between the 70 and 79 years of age. The male-to-female ratio in ulcerated lesions was 1.69, while in patients with non-ulcerated melanoma, the ratio was 1.28. This statistic follows the same pattern previously described in thin ulcerated melanoma lesions described by Hawkins *et al.* (7), with higher rates in white men 75 years old or older.

Ulcerated melanoma lesions were less frequently diagnosed in patients with private insurance and in Academic/Research programs, compared to non-ulcerated lesions. One possible explanation for this discrepancy may relate to relative knowledge of the disease, which could determine better prevention and earlier detection of melanoma.

Regarding the tumor characteristics analyzed in our study, ulcerated melanoma patients were more frequently diagnosed with a lesion in the extremities, with Breslow depth greater than 2 mm and AJCC stage II, III, or IV, and were more likely to experience a longer time to discharge. This may be due to the ulceration facilitating easier spread and aggressive behavior of the melanoma caused by a disruption of the epidermal basement membrane. Ulceration allows melanoma cells to penetrate deeper than the dermal-epidermal junction and causes overproduction of mediators that lead to further melanoma proliferation and metastasis (12).

Nevertheless, Hawkins *et al.* (7) recently observed that patients with ulcerated melanoma less than 1 mm thick have poorer survival compared to those with AJCC stage II tumors. Furthermore, in 2017, von Schuckmann *et al.* (13) observed that regular statin use could be a protective factor in patients affected by ulcerated melanoma.

A previous publication described ulcerated melanoma as more likely to be present in men with a mean age of 59 years, a deeper Breslow depth, and metastasis in a population in Spain (14). These findings suggest that the factors associated with the presence of ulceration may correspond to the biology of the disease independent of the population studied. However, in our large NCDB cohort analysis, ulcerated melanoma was found to be more likely in non-white men, living in rural areas and zip codes with low education and low income. We speculate that, as melanoma is less likely to appear in non-white patients, these patients may be diagnosed later at more advanced stages of disease and, as a consequence, with the presence of ulceration.

The strengths of this study are in the large sample taken from the NCDB, which records approximately 70% of the newly diagnosed cancer patients in the United States. Our analysis was conducted in multivariate logistic regression format to control for potential confounding factors, which many smaller studies on this topic are unable to portray.

Table I. Demographic and clinical data of patients with non-ulcerated or ulcerated melanoma.

Variable	Non-ulcerated N (%)	Ulcerated N (%)	p-Value ¹
Total	393,812 (85.8)	65,399 (14.2)	
Age ² , years	60.83 (16.10)	64.75 (16.21)	<0.001
Age group			<0.001
0-49	93,151 (23.7)	11,691 (17.9)	
50-59	79,627 (20.2)	11,464 (17.5)	
60-69	92,512 (23.5)	14,160 (21.7)	
70-79	78,563 (19.9)	14,316 (21.9)	
≥80	49,959 (12.7)	13,768 (21.1)	
Gender			<0.001
Male	220,980 (56.1)	41,057 (62.8)	
Female	172,832 (43.9)	24,342 (37.2)	
Race			<0.001
White	383,832 (97.5)	63,234 (96.7)	
Other	4,228 (1.1)	1,459 (2.2)	
Unknown	5,752 (1.5)	706 (1.1)	
Median household income			<0.001
<\$38,000	37,300 (9.5)	8,930 (13.7)	
\$38,000-\$47,999	75,651 (19.2)	14,798 (22.6)	
\$48,000-\$62,999	106,240 (27.0)	17,845 (27.3)	
≥\$63,000	171,454 (43.5)	23,036 (35.2)	
Unknown	3,167 (0.8)	790 (1.2)	
Education ³			<0.001
≥21.0%	33,431 (8.5)	8,450 (12.9)	
13.0%-20.9%	78,397 (19.9)	15,441 (23.6)	
7.0%-12.9%	136,914 (34.8)	22,656 (34.6)	
<7.0%	142,133 (36.1)	18,108 (27.7)	
Unknown	2,937 (0.7)	744 (1.1)	
Insurance status			<0.001
Uninsured	7,049 (1.8)	2,603 (4.0)	
Private	214,095 (54.4)	26,694 (40.8)	
Medicaid	7,621 (1.9)	2,582 (3.9)	
Medicare	153,260 (38.9)	31,774 (48.6)	
Other government	3,989 (1.0)	657 (1.0)	
Unknown	7,798 (2.0)	1,089 (1.7)	
Facility type			<0.001
Community Cancer Program	21,345 (5.4)	4,275 (6.5)	
Comprehensive Community Cancer Program	123,940 (31.5)	22,377 (34.2)	
Academic/Research Program	173,754 (44.1)	27,714 (42.4)	
Integrated Network Cancer Program	31,317 (8.0)	6,085 (9.3)	
Unknown	43,456 (11.0)	4,948 (7.6)	

¹p-Value estimated by χ^2 and Mann-Whitney tests. ²Data presented as mean (SD). ³Education is defined as percentage in zip code with no high school diploma.

However, studies on national patient databases also have limitations that merit consideration, such as missing data, the potential for coding errors, and the retrospective nature. Further analysis was restricted due to incomplete NCDB data regarding histologic subtype and tumor mitotic index, these factors were not available for inclusion in this analysis. Future directions for research in melanoma in this population

Table II. Odds of presenting tumor among melanoma patients¹.

Variable	OR	95% CI		p-Value
		Lower	Upper	
Gender				
Male	1	Reference	-	
Female	0.883	0.863	0.904	<0.001
Age, years				
0-49	1	Reference	-	
50-59	1.181	1.14	1.224	<0.001
60-69	1.26	1.215	1.307	<0.001
70-79	1.356	1.298	1.417	<0.001
≥80	1.747	1.668	1.829	<0.001
Race				
White	1	Reference	-	
Non-white	1.374	1.265	1.493	<0.001
Income				
<\$38,000	1	Reference	-	
\$38,000-\$47,999	0.965	0.926	1.005	0.083
\$48,000-\$62,999	0.955	0.915	0.996	0.032
≥\$63,000	0.954	0.91	1	0.048
Education				
≥21.0%	1	Reference	-	
13.0%-20.9%	0.897	0.862	0.935	<0.001
7.0%-12.9%	0.848	0.813	0.884	<0.001
<7.0%	0.777	0.741	0.814	<0.001
Insurance status				
Uninsured	1	Reference	-	
Private	0.564	0.529	0.6	<0.001
Medicaid	0.896	0.825	0.974	0.01
Medicare	0.621	0.58	0.664	<0.001
Other government	0.619	0.548	0.699	<0.001
Urban/Rural county				
Rural	1	Reference	-	
Metro	0.962	0.931	0.994	0.02
Urban	0.922	0.851	0.999	0.048
Body region				
Head and neck	1	Reference	-	
Trunk	1.299	1.26	1.339	<0.001
Extremities	1.338	1.3	1.377	<0.001
Other	0.219	0.198	0.242	<0.001

OR, Odds ratio; CI, confidence interval. ¹Logistic regression adjusted for characteristics of patients and tumors, including tumor behavior and American Joint Committee on Cancer Stage.

is warranted to explore more fully which contributing factors are associated with ulcerated melanoma.

In conclusion, our analysis indicated that patient disparities are associated with presence of ulcerated melanoma in the United States. Multivariate analysis adjusted for confounders demonstrated that age above 49 years, male sex, non-white race, living in rural areas, and living in zip codes with low income and low education were independently associated with presence of ulceration. We hope that this national database analysis may lay the groundwork for future clinical and translational studies to optimize ulcerated melanoma prognosis and treatment.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

DB, MTH, and AJF had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: DB, AJF, OJM, XL, ACS, SPB. Acquisition, analysis, or interpretation of data: DB, DJR, ACS, MTH and AJF. Drafting of the manuscript: DB, AS. Critical revision of the manuscript for important intellectual content: EG, SPB, MTH, ACS, OJM, XL, ASP, and AJF. Study supervision: AJF.

Acknowledgements

This study was supported in part by the Plastic Surgery Foundation, Mayo Clinic Center for Individualized Medicine and Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery .

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Received December 23, 2019

Revised January 8, 2020

Accepted January 10, 2020