ANTICANCER RESEARCH *41*: 2067-2070 (2021)
doi:10.21873/anticanres.14976

Treatment Contraindications Based on Comorbidity Status in Patients With Melanoma in the United States

DANIEL BOCZAR[1], SANJAY P. BAGARIA[2], AARON C. SPAULDING[3], MARIA T. HUAYLLANI[1], FRANCISCO R. AVILA[1], GUNEL GULIYEVA[1], XIAONA LU[4], BRIAN D. RINKER[1] and ANTONIO J. FORTE[1]

[1]*Division of Plastic Surgery, Mayo Clinic, Jacksonville, FL, U.S.A.;*
[2]*Department of Surgery, Mayo Clinic, Jacksonville, FL, U.S.A.;*
[3]*Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Jacksonville, FL, U.S.A.;*
[4]*Division of Plastic and Reconstructive Surgery, Yale School of Medicine, New Haven, CT, U.S.A.*

Abstract. *Background/Aim: Melanoma incidence has increased in the United States over the past few decades, and disparities in patient treatment have been described. Although most patients with melanoma are good candidates for curative treatment, some are considered poor candidates for treatment because of comorbid conditions. We examined whether patient demographics influence treatment contraindication in melanoma. Patients and Methods: The National Cancer Database (NCDB) was used to identify patients with melanoma from 2004 through 2015. Multivariate logistic regression was used to determine independent associations, adjusted for confounders. We excluded patients who did not receive treatment for reasons and patients with unknown treatment status. Results: A total of 499,092 patients met the inclusion criteria. Of these, 525 (0.1%) had Treatment contraindicated because of comorbid conditions (TCBC) and 498,567 (99.9%) received treatment. Multivariate logistic regression showed higher odds of TCBC in patients with government insurance (OR=1.34, 95%CI=03-1.73; p=0.03) and patients without insurance (OR=2.75, 95%CI=1.76-4.29; p<0.001) than patients with private insurance. Conclusion: Demographic disparities affects treatment decision in oncological patients. Our study demonstrated a significantly higher likelihood of "nontreatment because of comorbid conditions" among melanoma patients with government insurance or without insurance. Greater efforts are needed to address inequalities in melanoma treatment in the United States.*

Correspondence to: Antonio Jorge Forte, MD, Ph.D., Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, U.S.A. Tel: +1 9049532073, e-mail: ajvforte@yahoo.com.br

Key Words: Comorbidity, epidemiology, melanoma, National Cancer Database, treatment contraindications, United States.

Melanoma is an aggressive skin cancer and an important health issue worldwide (1). Melanoma incidence has increased in the United States over the past few decades, and disparities in patient treatment have been described (2-5). Surgical excision is essential for curative treatment of melanoma (6). Our aim was to analyze the characteristics associated with melanoma patients whose primary site surgery was not recommended or performed due to patient risk factors. We hypothesized that some patients may not receive needed treatment on the basis of modifiable factors.

Patients and Methods

This analysis was conducted with data from the National Cancer Database (NCDB), an initiative driven by the American Cancer Society and the American College of Surgeons' Commission on Cancer. The NCDB is a hospital based dataset and registers 70% of all cancer diagnoses in the United States (7). This study was considered nonregulated by the Mayo Clinic Institutional Review Board.

Data were extracted for all patients with a diagnosis of melanoma from January 1, 2004, through December 31, 2015. The cohort was then split into 2 groups: 1) "Surgery of primary site was performed"; or 2) "Surgery of primary site not recommended/performed due to patient risk factors." Patients were excluded if their surgery was not part of their planned treatment or if they refused surgery, died before surgery, or had unknown status regarding whether surgery was recommended or performed.

Demographic, facility, treatment, and tumor characteristics were collected. Patient demographic characteristics included age, sex, race/ethnicity, income (median household income of the patient's ZIP code), education (percentage of adults who did not graduate from high school in the patient's ZIP code), insurance status (uninsured or private or government insurance), and population density of the patient's ZIP code. Facility characteristics included facility type. Tumor characteristics included invasive tumor behavior, Breslow depth, American Joint Committee on Cancer stage, and location on the body. Presence of comorbid conditions was evaluated with the Charlson/Deyo Comorbidity Score [0 (no comorbidity), 1, or 2 or more].

Demographic, facility, treatment, and tumor characteristics were analyzed with the χ^2 or Mann-Whitney test, as appropriate.

Table I. *Patient demographics by surgical treatment indication.*

Variable	Treatment		Contraindicated comorbidity		*p*-Value
	N	%	N	%	
Total	498,567	99.9%	525	0.10%	
Age mean (SD)	61.37 (16.158)		69.63 (15.509)		<0.001
Gender					0.002
Male	283,903	56.9%	334	63.6%	
Female	214,664	43.1%	191	36.4%	
Insurance					<0.001
Private insurance	261,277	52.4%	136	25.9%	
Not insured	10,143	2.0%	31	5.9%	
Government	215,565	43.2%	347	66.1%	
Unknown	11,582	2.3%	11	2.1%	
Income					<0.001
Less than $38,000	50,033	10.0%	82	15.6%	
$38,000-$47,999	97,980	19.7%	137	26.1%	
$48,000-$62,999	134,693	27.0%	147	28.0%	
$63,000 +	211,520	42.4%	144	27.4%	
Unknown	4,341	0.9%	15	2.9%	
Education					<0.001
21% or more	45,711	9.2%	77	14.7%	
13%-20.9%	102,038	20.5%	140	26.7%	
7%-12.9%	172,919	34.7%	173	33.0%	
Less than 7%	173,851	34.9%	122	23.2%	
Unknown	4,048	0.8%	13	2.5%	
Populational density					0.029
Metro counties	409,641	82.2%	406	77.3%	
Urban counties	64,270	12.9%	83	15.8%	
Rural counties	8,130	1.6%	13	2.5%	
Missing	16,526	3.3%	23	4.4%	
Age					<0.001
0-49	113,843	22.8%	64	12.2%	
50-59	99,006	19.9%	69	13.1%	
60-69	115,778	23.2%	94	17.9%	
70-79	101,251	20.3%	133	25.3%	
80+	68,689	13.8%	165	31.4%	
Race					<0.001
Caucasian	485,171	97.3%	504	96.0%	
Non-caucasian	6,125	1.2%	17	3.2%	
Unknown	7,271	1.5%	4	0.8%	
Facility type					<0.001
Community Cancer Program	28,399	5.7%	46	8.8%	
Comprehensive Community Cancer Program	161,880	32.5%	228	43.4%	
Academic/Research Program	215,206	43.2%	172	32.8%	
Integrated Network Cancer Program	40,583	8.1%	55	10.5%	
Missing	52,499	10.5%	24	4.6%	
Charlson Deyo score					<0.001
No comorbidity	440,083	88.3%	377	71.8%	
Score of 1	48,055	9.6%	89	17.0%	
Score of 2 or more	10,429	2.1%	59	11.2%	

Qui-square test was used for categorical variables and *t*-test was used for numerical variables.

Multivariate analysis with logistic regression was performed to assess independent associations, adjusting for confounders. The outcome variable was "treatment contraindicated because of comorbid conditions (TCBC)" and the predicted variables were patient comorbid conditions (*i.e.*, Charlson/Deyo Comorbidity Score) and demographic characteristics (age, race/ethnicity, sex, and income, education, and population density based on the patient's ZIP code). Moreover, the logistic regression model was adjusted for potential tumor-related confounders (tumor stage, location on the body, and presence of metastasis). The significance level was set at $p<0.05$.

Statistical analysis was done with SPSS statistical software version 25.0 (SPSS Inc).

Results

A total of 499,092 patients met the study criteria in the National Cancer Database (NCDB) of Melanoma. Of these, 525 (0.1%) had treatment contraindicated because of comorbid conditions (TCBC) and 498,567 (99.9%) received treatment. Interestingly, 71.8% of the patients with TCBC had a Charlson/Deyo Comorbidity Score of 0. Patients with TCBC were older than those who received treatment (69.63±15.51 years *vs*. 61.37±16.16 years). Most patients with TCBC were men (63.6%) and had government insurance (66.1%), invasive tumor (94.9%), stage IV cancer (60.8%), and metastasis at diagnosis (53.5%) (Table I).

Multivariate logistic regression showed that older age and increased Charlson/Deyo Comorbidity Score were independently associated with higher odds of TCBC. However, we also observed higher odds of TCBC in patients with government insurance (OR=1.336, 95%CI=1.032-1.728; p=0.03) or without insurance (OR=2.751, 95%CI=1.764-4.290; p<0.001) than patients with private insurance. Patients with metastasis at diagnosis (OR=4.976, 95%CI=3.327-7.440; p<0.001), stage III cancer (OR=4.542, 95%CI=2.767-7.457; p<0.001), or stage IV cancer (OR=15.268, 95%CI=8.822-26.424; p<0.001) had higher odds of TCBC than patients with stage 0 cancer. Moreover, patients with tumors located in the trunk (OR=0.590, 95%CI=0.418-0.831; p=0.003) and extremities (OR=0.453, 95%CI=0.324-0.633; p<0.001) had lower odds of TCBC than patients with head and neck tumors (Table II).

Discussion

Patient demographics influence access to oncologic care (5, 9). We noted that 71.8% of patients with TCBC had a Charlson/Deyo Comorbidity Score of 0. Further analysis showed that type of insurance was an independent predictor of nontreatment. After adjustment for comorbid conditions and tumor severity, patients with government insurance or without insurance had higher odds of TCBC than patients with private insurance. Thus, our data suggest the need for efforts to address disparities in indications for melanoma treatment.

Authors have demonstrated the effect of health insurance on melanoma care (10, 11). Amini *et al*. (10) analyzed data from the Surveillance, Epidemiology, and End Results database to determine whether health insurance affected disease outcomes of 61,650 patients with melanoma. They noted that patients with Medicaid insurance or without insurance were more likely to have advanced disease at diagnosis and were less likely to receive curative treatment (10). In our analysis, patients with government insurance or without insurance had higher odds of TCBC than patients with private insurance.

Table II. *Odds of having surgery contraindicated due to presence of risk factor.*

		95% C.I. for EXP(B)		*p*-Value
Variables	OR	Lower	Upper	
Age	1.031	1.022	1.039	<0.001
Gender				
Male	1	Reference	-	
Female	1.129	0.926	1.377	0.232
Income				
Less than $38,000	1	Reference	-	
$38,000-$47,999	1.078	0.777	1.495	0.652
$48,000-$62,999	0.959	0.675	1.361	0.813
$63,000 +	0.776	0.52	1.158	0.214
Unknown	7.749	1.372	43.751	0.02
Education				
21% or more	1	Reference	-	
13%-20.9%	1.123	0.811	1.556	0.484
7%-12.9%	1.11	0.786	1.568	0.554
Less than 7%	1.039	0.694	1.554	0.854
Unknown	0.261	0.039	1.738	0.165
Race				
Caucasian	1	Reference	-	
Non-caucasian	1.391	0.799	2.423	0.243
Unknown	0.752	0.269	2.096	0.585
Insurance status				
Private insurance	1	Reference	-	
Not insured	2.751	1.764	4.29	<0.001
Government insurance	1.336	1.032	1.728	0.028
Unknown	1.057	0.548	2.039	0.869
Charlson-Deyo comorbidity score				
No comorbidity	1	Reference	-	
Score of 1	1.352	1.043	1.752	0.023
Score of 2 or more	2.265	1.625	3.157	<0.001
Tumor stage				
Stage 0	1	Reference	-	
Stage I	0.456	0.247	0.843	0.012
Stage II	1.57	0.903	2.729	0.11
Stage III	4.542	2.767	7.457	<0.001
Stage IV	15.268	8.822	26.424	<0.001
Stage unknown	5.022	3.131	8.056	<0.001
Metastasis				
No	1	Reference	-	
Yes	4.976	3.327	7.44	<0.001
Unknown	5.299	3.711	7.567	<0.001
Populational density				
Metro counties	1	Reference	-	
Urban counties	1.054	0.799	1.39	0.712
Rural counties	1.592	0.862	2.941	0.137
Missing	0.977	0.53	1.798	0.94
Tumor location				
Head and neck	1	Reference	-	
Trunk	0.59	0.418	0.831	0.003
Extremities	0.453	0.324	0.633	<0.001
Other	17.791	13.624	23.233	<0.001

Multivariate logistic regression for "treatment contraindicated due to comorbidities" accounting for patient demographic and tumor characteristics. OR, Odds ratio; CI, confidence interval.

Treatment delays have been associated with increased risks of comorbid conditions and death among cancer patients (12-15). Adamson *et al*. (11) demonstrated disparities in surgical treatment delays in a cohort of 7,629 patients with melanoma and included in the North Carolina Cancer Registry from 2004 through 2011. They noted that patients with private insurance experienced less delay in treatment than patients with Medicaid insurance (11).

Studies of national cancer databases are limited by their retrospective nature, missing data, and possibility of inaccurate data records. We were unable to account for histologic subtype and tumor mitotic index, limiting further analysis of tumor severity in patients with TCBC. Moreover, the NCDB only includes patients treated at hospitals. Nonetheless, the NCDB includes approximately 70% of the oncologic patients in the United States, thus providing this study with enough statistical power for multivariate logistic regression and to control for relevant confounding factors such as tumor characteristics. We encourage future investigations of TCBC in patients with melanoma, as well as how to promote clinical guidelines for fair administration of melanoma care, regardless of patient demographic characteristics.

Conclusion

Demographic disparities may influence the decision not to treat a patient because of comorbidities. Multivariate analysis, adjusted for confounders, showed that patients with government insurance or without insurance were more likely to have treatment contraindicated because of comorbid conditions. We hope that this finding supports future translational initiatives to reduce disparities in melanoma care.

Conflicts of Interest

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

Authors' Contributions

DB, MTH, GG, FRA, 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, SPB, ACS, XL, BDR. Acquisition, analysis, or interpretation of data: DB, MTH, FRA, GG, and AJF. Drafting of the manuscript: DB, MTH, FRA, GG, ACS. Critical revision of the manuscript for important intellectual content: SPB, ACS, XL, BDR, AJF. Study supervision: AJF.

Acknowledgements

This study was supported in part by the Plastic Surgery Foundation, Mayo Clinic Center for Individualized Medicine and Mayo Clinic Center for Regenerative Medicine.

References

1 Guy GP, Jr., Thomas CC, Thompson T, Watson M, Massetti GM and Richardson LC: Vital signs: Melanoma incidence and mortality trends and projections – United States, 1982-2030. MMWR Morb Mortal Wkly Rep *64(21)*: 591-596, 2015. PMID:26042651.

2 Al-Qurayshi Z, Srivastav S, Wang A, Boh E, Hamner J, Hassan M and Kandil E: Disparities in the presentation and management of cutaneous melanoma that required admission. Oncology *95(2)*: 69-80, 2018. PMID: 29913445. DOI: 10.1159/000468152

3 Gardner L, Strunck J, Wu Y and Grossman D: Current controversies in early-stage melanoma. Journal of the American Academy of Dermatology *80(1)*: 1-12, 2020. DOI: 10.1016/j.jaad.2018.03.053

4 Boczar D, Restrepo D, Sisti A, Huayllani M, Saleem H, Lu X, Cinotto G, Manrique O, Spaulding A and Forte A: Analysis of melanoma in African American patients in the United States. Anticancer Research *39(11)*: 6333-6337, 2019. DOI: 10.21873/anticanres.13844

5 Restrepo DJ, Huayllani MT, Boczar D, Sisti A, Gabriel E, Lemini R, Spaulding AC, Bagaria S, Manrique OJ and Forte AJ: Biopsy type disparities in patients with melanoma: Who receives the standard of care? Anticancer Res *39(11)*: 6359-6363, 2019. PMID: 31704868. DOI: 10.21873/anticanres.13848

6 Joyce D and Skitzki J: Surgical management of primary cutaneous melanoma. Surgical Clinics of North America *100(1)*: 61-70, 2019. DOI: 10.1016/j.suc.2019.09.001

7 Bilimoria K, Stewart A, Winchester D and Ko C: The national cancer data base: A Powerful initiative to improve cancer care in the United States. Annals of Surgical Oncology *15(3)*: 683-690, 2020. DOI: 10.1245/s10434-007-9747-3

8 Liu X, Langsdon S, Holloway W, Xu S, Tang Q, Xu Y, Velamuri S and Hickerson W: The ethics of facial allotransplantation. Plastic and Reconstructive Surgery – Global Open *7(10)*: e2425, 2021. DOI: 10.1097/gox.0000000000002425

9 Restrepo D, Boczar D, Huayllani M, Sisti A, Gabriel E, Mclaughlin S, Bagaria S, Spaulding A, Rinker B and Forte A: Influence of race, income, insurance, and education on the rate of breast reconstruction. Anticancer Research *39(6)*: 2969-2973, 2019. DOI: 10.21873/anticanres.13428

10 Amini A, Rusthoven C, Waxweiler T, Jones B, Fisher C, Karam S and Raben D: Association of health insurance with outcomes in adults ages 18 to 64 years with melanoma in the United States. Journal of the American Academy of Dermatology *74(2)*: 309-316, 2018. DOI: 10.1016/j.jaad.2015.09.054

11 Adamson A, Zhou L, Baggett C, Thomas N and Meyer A: Association of delays in surgery for melanoma with insurance type. JAMA Dermatology *153(11)*: 1106, 2017. DOI: 10.1001/jamadermatol.2017.3338

12 Bardell T, Belliveau P, Kong W and Mackillop W: Waiting times for cancer surgery in ontario: 1984-2000. Clinical Oncology *18(5)*: 401-409, 2019. DOI: 10.1016/j.clon.2006.02.012

13 Bilimoria K, Ko C, Tomlinson J, Stewart A, Talamonti M, Hynes D, Winchester D and Bentrem D: Wait times for cancer surgery in the United States. Annals of Surgery *253(4)*: 779-785, 2021. DOI: 10.1097/SLA.0b013e318211cc0f

14 Korsgaard M, Pedersen L, Sørensen H and Laurberg S: Delay of treatment is associated with advanced stage of rectal cancer but not of colon cancer. Cancer Detection and Prevention *30(4)*: 341-346, 2020. DOI: 10.1016/j.cdp.2006.07.001

15 Spurgeon P, Barwell F and Kerr D: Waiting times for cancer patients in england after general practitioners' referrals: Retrospective national survey. Bmj *320(7238)*: 838-839, 2000. PMID:10731176.

Received February 7, 2021
Revised February 24, 2021
Accepted March 3, 2021