

Residual Tumor on Wide Excisional Margins After Treatment of Invasive Melanoma

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Abstract. *Background/Aim: The surgical management of invasive melanoma has been debated for many years and recommended excisional margins have been established. We aimed to describe the factors and survival related to the presence of residual tumor in patients with invasive melanoma lymph nodes negative. Patients and Methods: We performed a retrospective study by querying the National Cancer Database from 2004 to 2015. Associations were tested using a multivariate analysis. Overall survival was compared using the Kaplan-Meier method. Results: A total of 26,440 patients met the inclusion criteria. For Breslow depth groups ≤ 1 mm and > 2 mm, older age and location in the head and neck were factors associated to residual tumor in margins ($p < 0.05$), whereas only location in the head and neck was associated to residual tumor for patients with Breslow depth between 1.01-2.00 mm ($p < 0.05$). Conclusion: Knowledge of the factors associated with the residual tumor will help establish a patient-centered management and decrease the recurrence of disease.*

Almost ten thousand patients per year are affected with melanoma around the world and the number of cases is increasing over time (1-4). Wide local excision surgery is the most recommended procedure for invasive melanoma and is associated with a cure rate of approximately 80% in the United States (5).

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Multiple clinical trials have supported the current National Comprehensive Cancer Network (NCCN) guidelines that recommend specific excisional margins for wide resection of invasive melanomas in an attempt to decrease recurrence of the disease (6-11). Despite these recommendations, the presence of recurrence of disease still prevails. A possible and common cause of disease recurrence is the presence of residual tumor on margins after treatment. However, to date there is a lack of knowledge on the factors associated to the presence of residual tumor margins after treatment of invasive melanomas.

In this study, we sought to find the factors and 10-year overall survival (OS) related to the presence of residual tumor on margins after excisional surgery in patients with lymph node-negative invasive melanoma diagnosed from 1st January 2004 to 31th December 2015 in the United States.

Patients and Methods

We performed a retrospective cohort study by querying the National Cancer Database (NCDB) between 2004 and 2015. A total of 525,271 patients were diagnosed with melanoma. Only patients with lymph node-negative invasive melanomas and who underwent wide excisional surgery were included in the study. We excluded patients with missing information in the factors analyzed and with Stage misclassification according to the American Joint Committee on Cancer (AJCC) to only consider patients with primary local invasive melanoma without metastasis. Only 26,440 patients met inclusion criteria and were considered for analysis. We considered sex, age, comorbidities, tumor site, ulceration, stage, facility type and excisional margins as independent variables while residual tumor after resection was considered the dependent variable.

Statistical analysis. We performed a χ^2 analysis to compare the characteristics of patients with presence or absence of residual tumor in margins after tumor resection in each of the following Breslow depth: 1.00 mm or less, 1.01 to 2.00 mm, 2.01 to 4.00 mm,

and more than 4 mm. A multivariate logistic regression analyzed the factors associated with presence of residual tumor in each Breslow depth group. Kaplan-Meier survival curves compared 10-year OS in patients with presence *versus* absence of residual tumor on margins after the surgical resection in each Breslow depth group. A statistical difference between the survival curves was determined with Log-rank test. A *p*-value lower than 0.05 and a CI of 95% were considered significant for all analyses. Data were analyzed using SPSS, version 25 (SPSS, Inc, an IBM Company, Chicago, IL, USA) software.

Results

We found significant differences in percentages of residual tumor by excisional margins, age, comorbidities, and tumor location in some of the Breslow depth groups ($p < 0.05$) (Table I).

Patients more than 80 years old and with melanomas located in the head and neck were more likely to have residual tumor on margins for Breslow depth groups 1 mm or less and more than 2 mm ($p < 0.05$), whereas for patients in the Breslow depth group between 1.01 mm and 2 mm, location of melanomas in the head and neck was the only factor significantly associated with having residual tumor on margins (Table II). Our study did not find any significant difference in the likelihood to present residual tumor by excisional margins in the Breslow depth group deeper than 1 mm. However, we found that patients who underwent excisional surgery with wider margins were more likely to have residual tumor on margins after surgery in the Breslow depth group, 1 mm or less (OR=1.92; 95% CI=1.28-2.89; $p=0.002$) (Table II).

Overall survival. Ten-year OS was found for each Breslow depth group and compared by the absence or presence of residual tumor (Figure 1). No significant difference was found in 10-year OS by absence or presence of residual tumor in Breslow depths of 1 mm or less (68% *vs.* 43%, $p=0.05$), 1.01 to 2.00 mm (58% *vs.* 67%, $p=0.59$), or deeper than 4.00 mm (27% *vs.* 34%, $p=0.16$). However, we found a statistically significant difference in Breslow depth group, 2.01 to 4.00 mm (44% *vs.* 25%, $p=0.01$).

Discussion

Our study showed that older patients and those with invasive melanomas located in the head and neck were more likely to have residual tumor on margins after surgical excision. These results are supported by Mangold *et al.* (12) who found that residual tumor in the margins was more likely to be present in older patients with thicker tumors located in the head and neck region. The explanation of this finding was the difficulty in delineating surgical margins on the heavily sun-damaged skin in addition to the decreased immune function found in older patients.

We did not find any significant differences in the likelihood to present residual tumor by excisional margins in almost all the Breslow depth groups, with the exception of patients with invasive melanoma of 1 mm thick or less who had excisional margins wider than 2 cm, in which we found they were more likely to have residual tumor after surgery. We believe that this last finding may correspond to the presence of microscopic satellites or in-transit metastases (13). "Microscopic satellites" have been known to be discrete and discontinuous tumor nests more than 0.05 mm in diameter and separated from the main tumor by the reticular dermal collagen or subcutaneous fat by a distance of at least 0.3 mm (14). In-transit metastases are nests of tumor cells at least 2 cm distant from the primary lesion that have not reached the closest lymph node (15). Although these lesions are classified as stage III disease and our study only reviewed patients with stages I or II, presence of microscopic satellites or in-transit metastases often are not evident or classified correctly (16). Hence, presence of these lesions may explain residual tumor after excisional margins wider than 2 cm. Another potential explanation is the discontinuous spreading of malignant melanocytes around the melanoma in a non-confluent pattern may favor the finding of residual tumor in margins (17). Miller *et al.* (18) described that more than 1 diagnostic biopsy carried more risk for positive tumors in margins, suggesting this was due to the increased ability to delineate and define the lesion. On the other hand, some studies suggest that wider-than-recommended margins are ligated to decreasing rates of recurrence, such as McKinnon *et al.* (19) who found an inverse relation between wider excisional margins and recurrence of disease in melanomas 2 mm thick or less.

We also observed a statistically significant difference in 10-year OS between patients with presence or absence of residual tumor in the margins after surgery in the Breslow depth group of 2.01 to 4.00 mm. This difference was not found in the other Breslow depth groups, probably because after surgeons realized that patients had residual tumor on margins, patients underwent a second surgery to remove the remaining tumor. The difference found in the Breslow depth group of 2.01 to 4.00 mm may be due to the influences of the factors that we found associated with 10-year OS such as age, sex, comorbidities, location of tumor, and ulceration. Patients with residual tumor, in this Breslow depth group, were significantly older, with comorbidities, and with ulcerated melanomas located in the head and neck compared with patients without residual tumor.

This study is not without limitations and include those involved in retrospective analyses. We only considered invasive melanoma patients with no lymph node involvement to decrease the chances of residual tumor due to disease stage. Moreover, a very strict inclusion and exclusion criteria was done in order to avoid misclassifications. Although, we were

Table 1. Descriptive statistics by residual tumor for each Breslow depth.

	Breslow Depth ≤1.00 mm			Breslow Depth 1.01-2.00 mm			Breslow Depth 2.01-4.00 mm			Breslow Depth >4.00 mm		
	No residual tumor (N=7,087)	Residual tumor (N=95)	p-Value	No residual tumor (N=10,115)	Residual tumor (N=112)	p-Value	No residual tumor (N=5,713)	Residual tumor (N=76)	p-Value	No residual tumor (N=3,159)	Residual tumor (N=83)	p-Value
Excisional Margins			0.001			0.627			0.735			0.896
Margins >1 cm and ≤2 cm	4,895 (69.1%)	51 (53.7%)		7,343 (72.6%)	79 (70.5%)		3,956 (69.2%)	54 (71.1%)		2,077 (65.7%)	54 (65.1%)	
Margins >2 cm	2,192 (30.9%)	44 (46.3%)		2,772 (27.4%)	33 (29.5%)		1,757 (30.8%)	22 (28.9%)		1,082 (34.3%)	29 (34.9%)	
Gender			0.403			0.260			0.092			0.017
Male	4,099 (57.8%)	59 (62.1%)		6,062 (59.9%)	73 (65.2%)		3,678 (64.4%)	56 (73.7%)		2,117 (67.0%)	66 (79.5%)	
Female	2,988 (42.2%)	36 (37.9%)		4,053 (40.1%)	39 (34.8%)		2,035 (35.6%)	20 (26.3%)		1,042 (33.0%)	17 (20.5%)	
Age			<0.001			0.351			0.005			0.043
40-60 years	3,629 (51.2%)	28 (29.5%)		4,546 (44.9%)	43 (38.4%)		1,992 (34.9%)	13 (17.1%)		989 (31.3%)	17 (20.5%)	
61-80 years	3,063 (43.2%)	51 (53.7%)		4,774 (47.2%)	58 (51.8%)		2,963 (51.9%)	49 (64.5%)		1,629 (51.6%)	45 (54.2%)	
>80 years	395 (5.6%)	16 (16.8%)		795 (7.9%)	11 (9.8%)		758 (13.3%)	14 (18.4%)		541 (17.1%)	21 (25.3%)	
Comorbidities			0.180			0.157			0.038			0.954
No	6,152 (86.8%)	78 (82.1%)		8,643 (85.4%)	101 (90.2%)		4,728 (82.8%)	56 (73.7%)		2,542 (80.5%)	67 (80.7%)	
Yes	935 (13.2%)	17 (17.9%)		1,472 (14.6%)	11 (9.8%)		985 (17.2%)	20 (26.3%)		617 (19.5%)	16 (19.3%)	
Location			<0.001			<0.001			<0.001			0.001
Head and Neck, Skin NOS and overlapping lesion	988 (13.9%)	29 (30.5%)		1,518 (15.0%)	38 (33.9%)		1,115 (19.5%)	28 (36.8%)		833 (26.4%)	37 (44.6%)	
Trunk	2,717 (38.3%)	27 (28.4%)		3,463 (34.2%)	25 (22.3%)		1,709 (29.9%)	13 (17.1%)		993 (31.4%)	18 (21.7%)	
Extremities	3,382 (47.7%)	39 (41.1%)		5,134 (50.8%)	49 (43.8%)		2,889 (50.6%)	35 (46.1%)		1,333 (42.2%)	28 (33.7%)	
Ulceration			0.873			0.08			0.742			0.979
No ulceration	6,457 (91.1%)	87 (91.6%)		8,241 (81.5%)	84 (75.0%)		3,414 (59.8%)	44 (57.9%)		1,451 (45.9%)	38 (45.8%)	
Ulceration present	630 (8.9%)	8 (8.4%)		1,874 (18.5%)	28 (25.0%)		2,299 (40.2%)	32 (42.1%)		1,708 (54.1%)	45 (54.2%)	
Facility type			0.230			0.56			0.620			0.490
Non-Academic/ Research Program	4,307 (60.8%)	52 (54.7%)		5,049 (49.9%)	59 (52.7%)		2,720 (47.6%)	34 (44.7%)		1,491 (47.2%)	36 (43.4%)	
Academic/ Research Program	2,780 (39.2%)	43 (45.3%)		5,066 (50.1%)	53 (47.3%)		2,993 (52.4%)	42 (55.3%)		1,668 (52.8%)	47 (56.6%)	

NOS, Not otherwise specified.

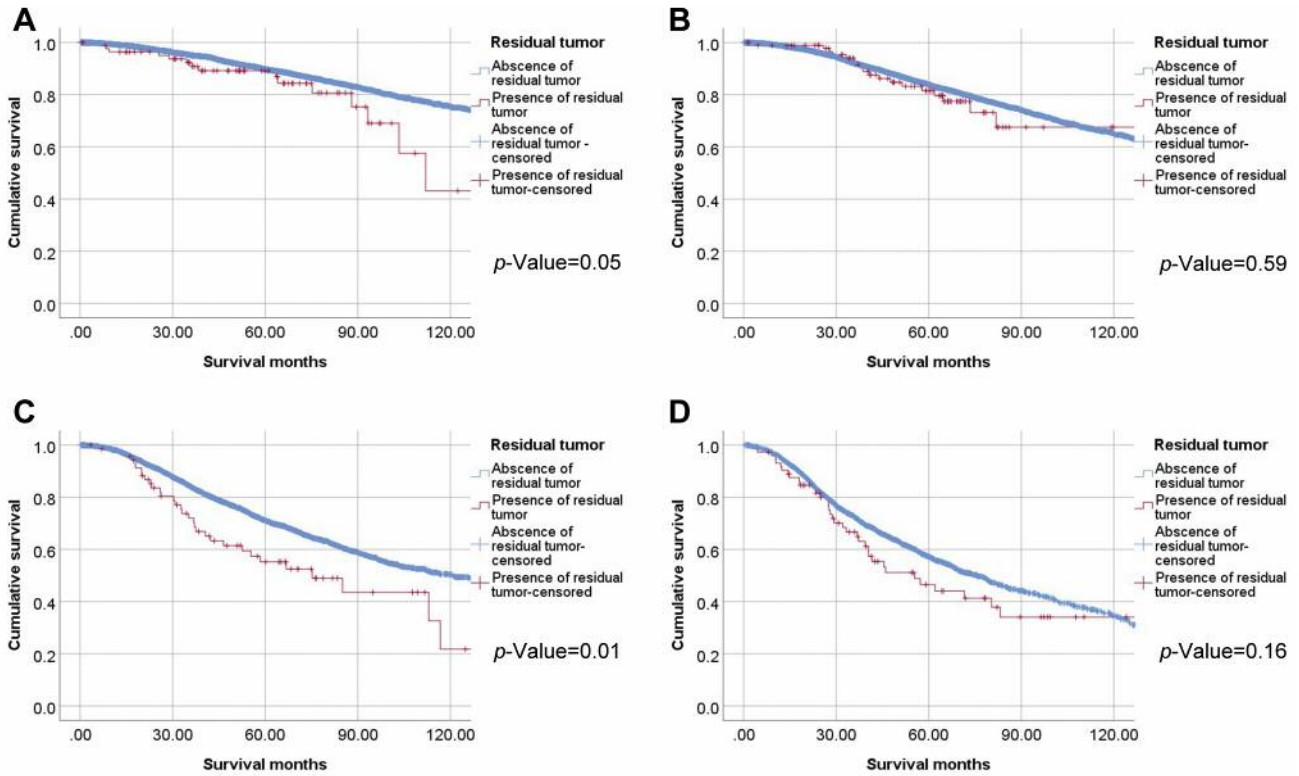


Figure 1. 10-Year overall survival according to residual tumor. (A) Breslow depth ≤ 1 mm. (B) Breslow depth 1.01-2 mm. (C) Breslow depth 2.01-4 mm. (D) Breslow depth > 4 mm.

Table II. Multivariable logistic regression models for presence of residual tumor for each Breslow group.

Variables	Breslow ≤ 1.00 mm		Breslow 1.01-2.00 mm		Breslow 2.01-4.00 mm		Breslow > 4.00 mm	
	OR (LCL, UCL)	p-Value	OR (LCL, UCL)	p-Value	OR (LCL, UCL)	p-Value	OR (LCL, UCL)	p-Value
Female	1.03 (0.66, 1.61)	0.88	0.92 (0.61, 1.39)	0.68	0.74 (0.43, 1.26)	0.27	0.56 (0.32, 0.98)	0.04
61-80 years old	1.97 (1.23, 3.16)	0.005	1.15 (0.77, 1.73)	0.49	2.15 (1.15, 4.00)	0.02	1.43 (0.81, 2.54)	0.22
>80 years	4.45 (2.33, 8.52)	<0.001	1.20 (0.61, 2.37)	0.60	2.28 (1.05, 4.92)	0.04	2.09 (1.08, 4.03)	0.03
Comorbidities	1.11 (0.64, 1.91)	0.71	0.58 (0.31, 1.10)	0.10	1.55 (0.92, 2.61)	0.10	0.94 (0.54, 1.65)	0.83
Head and Neck, Skin NOS, and overlapping lesion	2.14 (1.28, 3.57)	0.004	2.52 (1.61, 3.96)	<0.001	1.80 (1.07, 3.04)	0.03	1.86 (1.12, 3.10)	0.02
Trunk	0.90 (0.54, 1.50)	0.69	0.75 (0.46, 1.23)	0.25	0.63 (0.33, 1.21)	0.16	0.81 (0.44, 1.48)	0.48
Ulceration Present	0.84 (0.40, 1.75)	0.64	1.41 (0.91, 2.17)	0.12	1.06 (0.67, 1.68)	0.81	1.07 (0.69, 1.66)	0.77
Academic/Research Program	1.21 (0.80, 1.82)	0.38	0.85 (0.58, 1.24)	0.39	1.12 (0.71, 1.78)	0.62	1.19 (0.76, 1.86)	0.45
Margins > 2 cm	1.92 (1.28, 2.89)	0.002	1.09 (0.73, 1.65)	0.67	0.96 (0.58, 1.58)	0.87	1.09 (0.69, 1.74)	0.70

OR, Odds ratio; LCL, lower confidence limit; UCL, upper confidence limit.

unable to address recurrence of disease due to lack of information in the NCDB, we examined the variable residual tumor on margins after surgery, as a measure of the persistence of disease. Despite these limitations, we believe this study reports a valuable analysis of factors associated with the likelihood to have residual tumor on margins after surgery in patients with lymph node-negative invasive melanoma.

In conclusion, we found that older patients and melanomas located on the head and neck are more likely to have residual tumor on margins after treatment. Possible unobserved presence of microscopic satellites or in-transit metastases at disease staging may be a cause of positive radial margins when taking wider excisional margins in patients with invasive melanoma of 1 mm thick or less.

Differences in 10-year OS by excisional margins and presence of residual tumor for all Breslow depth groups were not statistically significant, with the exception of the 2.01 to 4.00 mm group, where residual tumor in radial margins after surgery was an independent predictor factor of 10-year OS.

Conflicts of Interest

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

Authors' Contributions

MTH, SPB 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: MTH, AJF, ACS, JJC. Acquisition, analysis, or interpretation of data: JJC, ASP, MTH, AJF. Drafting of the article: MTH, SPB, DJR, DB, AS. Critical revision of the article for important intellectual content: SPB, EMG, BR, ACS and AJF. Study supervision: AJF

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