

Wide Excisional Surgery in Invasive Melanoma Treatment: Factors Driving Non-compliance With National Guidelines

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Abstract. *Background/Aim: Margin size during wide excisional surgery for invasive melanoma treatment have been established by national guidelines. This study identified factors associated with wider than recommended excisional margins and its impact on survival. Patients and Methods: The National Cancer Database was queried to identify patients with primary invasive melanoma. Statistical analysis was performed using univariate and multivariate analysis. Overall survival was compared using Kaplan–Meier method. Results: A total of 26,440 patients were included in the analysis. Melanomas located on the trunk were more likely to be treated using wider than recommended excisional margins for certain Breslow depth groups ($p<0.05$), while the opposite was true for those being treated in an academic/research program ($p<0.05$). The practice of taking wider than recommended margins was not associated with improved survival. Conclusion: Tumor location and facility type influence non-compliance with the National Comprehensive Cancer Network guidelines. Lack of survival benefit in patients with wider excisional margins seems to support guideline recommendations.*

Melanoma affects approximately 10,000 people per year around the world (1). Wide local excision surgery is the most recommended procedure for melanoma and is associated with a cure rate of approximately 80% in the United States

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(2). Results from multiple clinical trials have helped inform guidelines on margins based on the Breslow depth to reduce recurrence of disease (3-8). Lower rates of local and regional recurrence were associated with narrower excisional margins (7). On the other hand, wider excisional margins resulted in compromising of the cosmesis, limitation of function, and additional hospital stays due to skin graft and skin flap procedures, resulting in an increase in morbidity (9, 10).

To avoid poor survival and unesthetic outcomes, the National Comprehensive Cancer Network (NCCN) has standardized the length of the excisional margins that must be taken (11). To our knowledge, there is no report assessing the factors that drive non-compliance with these guidelines.

In this study, we investigated compliance with these guidelines, in addition to the factors and 10-year overall survival (OS) related to the use of wider than recommended excisional radial margins in patients with lymph node-negative invasive melanoma diagnosed from 1st January 2004 to 31th December 2015 in the United States.

Patients and Methods

A retrospective cohort study was conducted of melanoma hospital registry data registered in the National Cancer Database (NCDB) between 2004 and 2015.

Inclusion and exclusion criteria. We identified 525,271 patients with melanoma diagnosed during the study period. We excluded patients with melanoma in situ, those with lymph node positivity, those who underwent procedures other than wide excisional surgery, those who did not have surgery on the primary site, and those for whom information was missing from the registry. Finally, we excluded patients classified as having stage 0 or IV, and T0, Tis, or M1 in the seventh edition of the TNM classification by the American Joint Committee on Cancer (12) in order only to consider patients with primary local invasive melanoma without metastasis.

The 34,259 patients included were divided by Breslow depth into four groups: 1.00 mm or less, 1.01 to 2.00 mm, 2.01 to 4.00 mm, and deeper than 4.00 mm. From each group, we then excluded patients with any type of missclassification. In the end, 26,440 patients met the inclusion criteria and were considered for analysis.

Variables. Independent variables included sex, age, comorbidities, tumor site, ulceration, stage, and facility type. Dependent variable of interest was the excisional margins. Patients were divided into two groups based on the width of radial margins measured microscopically: Wider than 1 cm but no more than 2 cm, and wider than 2 cm. Patients with less than 1 cm margins were not considered because the NCDB did not have any information regarding this group.

Statistical analysis. A chi-squared analysis was performed to compare the percentages of patients with excisional margins of wider than 1 cm but no more than 2 cm and wider than 2 cm for each of the Breslow depth groups. Univariate and multivariate logistic regression was performed to analyze the factors associated with wider than recommended excisional margins.

Kaplan–Meier survival curves were used to compare 10-year OS of patients with invasive melanoma with and without wider than recommended excisional margins. Log-rank test was used to determine statistical difference between the survival curves. A *p*-value lower than 0.05 and a confidence interval of 95% were considered significant for all analyses. Data were analyzed using SPSS, version 25 (IBM, Armonk, NY, USA) software.

Results

Excisional margins. Of patients with Breslow depth of 1.00 mm or less, 7,182 underwent wider than recommended margins (>1 cm). On the other hand, for patients with Breslow depth of 1.01 to 2.00 mm, 2.01 to 4.00 mm, and deeper than 4.00 mm, 2,805 (27.4%), 1,779 (30.7%), and 1,111 (34.3%) patients underwent wider than recommended margins (>2 cm), respectively (Table I).

The most common tumor sites in all groups were the extremities, followed by trunk and head and neck including overlapping lesions. Furthermore, most patients did not present with ulceration in their lesions. We noticed a significant difference in the percentage of patients with Breslow depth more than 1.00 mm between facility types, according to excisional surgical margins ($p<0.001$) (Table I).

Table II documents the characteristics that determine taking more than 2 cm surgical excisional margins. We found that melanoma located on the trunk was more likely to undergo surgery with wider excisional margins in patients with Breslow depth of 1.00 mm or less [odds ratio (OR)=1.14, 95% CI=1.02-1.28; $p=0.02$] and 1.01 to 2.00 mm (OR=1.13, 95% CI=1.02-1.25; $p=0.02$) compared to those located on the extremities. In addition, patients involved in academic/research programs were less likely to have wider than recommended excisional margins in Breslow depth groups 1.01 to 2.00 mm (OR=0.66, 95% CI=0.60-0.72; $p<0.001$), 2.01 to 4.00 mm (OR=0.61, 95%

CI=0.55-0.69; $p<0.001$), and deeper than 4.00 mm (OR=0.70, 95% CI=0.60-0.81; $p<0.001$).

Overall survival. Ten-year OS was compared for each Breslow depth group according to excisional surgical margins (Figure 1). We did not find significant differences in 10-year OS by excisional margins for any of the groups.

Discussion

Our study demonstrated that a high number of patients underwent surgery with wider than recommended margins for each Breslow depth. A possible cause of this is that surgical excision is surgeon-dependent. Most surgeons agree that they should measure the margins from the periphery of the primary lesion and then extend radially; however, in most cases this is merely intuitive and not well defined (2, 9). Moreover, we found that for patients with melanoma of Breslow depth of 2 mm or less, lesions located in the trunk were more likely to undergo wider excision. The site of the melanoma might influence the surgeon's decision on margins. This decision is usually guided by the desire to cure and reduce recurrence of the disease, without much consideration for reconstruction after excision, and taking into account that melanomas located in the trunk can easily be hidden. In addition, patients with a Breslow depth greater than 2 mm treated in academic/research programs were more likely to have wider than recommended margins. This may be related to a greater disposition of health professionals to carry out established treatment protocols as they are more involved in education and research (13).

We found no statistically significant differences in 10-year OS when comparing the Breslow depth groups by the two excisional margin groups. This finding suggests that performing wider than recommended margins in patients with Breslow depth greater than 1 mm will not improve survival. We cannot state the same for patients with a Breslow depth of 1 mm or less because the comparison did not include patients who underwent surgery with the NCCN's recommended excisional margins (1 cm). However, based on this result, we strongly advocate that NCCN recommendations guide surgical decision regarding excisional margins. Furthermore, in light of our finding that, independently of tumor location, facility type was associated with noncompliance, effort should be made to train and update all surgeons who commonly see patients with melanoma.

This study is not without limitations, which include those involved in retrospective analyses. We decided to study patients with invasive melanoma with no lymph node involvement in order to reduce the chances of wider than recommended margins being due to disease stage. For that reason, we established very strict inclusion and exclusion criteria, trying to match the stage of the disease with the

Table I. Descriptive statistics [n (%)] for each Breslow group by excisional margins.

Variable	Breslow ≤1.00 mm			Breslow 1.01-2.00 mm			Breslow 2.01-4.00 mm			Breslow >4.00 mm		
	>1-2 cm (N=4,946)	>2 cm (N=2,236)	p-Value	>1-2 cm (N=7,422)	>2 cm (N=2,805)	p-Value	>1-2 cm (N=4,010)	>2 cm (N=1,779)	p-Value	>1-2 cm (N=2,131)	>2 cm (N=1,111)	p-Value
Gender												
Male	2,880 (58.2%)	1,278 (57.2%)	0.394	4,440 (59.8%)	1,695 (60.4%)	0.577	2,562 (63.9%)	1,172 (65.9%)	0.144	1,421 (66.7%)	762 (68.6%)	0.273
Female	2,066 (41.8%)	958 (42.8%)		2,982 (40.2%)	1,110 (39.6%)		1,448 (36.1%)	607 (34.1%)		710 (33.3%)	349 (31.4%)	
Age												
40-60 years	2,548 (51.5%)	1,109 (49.6%)	0.226	3,343 (45.0%)	1,246 (44.4%)	0.709	1,353 (33.7%)	652 (36.6%)	0.073	659 (30.9%)	347 (31.2%)	0.903
61-80 years	2,111 (42.7%)	1,003 (44.9%)		3,503 (47.2%)	1,329 (47.4%)		2,124 (53.0%)	888 (49.9%)		1,098 (51.5%)	576 (51.8%)	
>80 years	287 (5.8%)	124 (5.5%)		576 (7.8%)	230 (8.2%)		533 (13.3%)	239 (13.4%)		374 (17.6%)	188 (16.9%)	
Comorbidities												
No	4,308 (87.1%)	1,922 (86.0%)	0.186	6,360 (85.7%)	2,384 (85.0%)	0.370	3,336 (83.2%)	1,448 (81.4%)	0.096	1,727 (81.0%)	882 (79.4%)	0.260
Yes	638 (12.9%)	314 (14.0%)		1,062 (14.3%)	421 (15.0%)		674 (16.8%)	331 (18.6%)		404 (19.0%)	229 (20.6%)	
Location												
Head and neck, skin NOS, overlapping lesion	710 (14.4%)	307 (13.7%)	0.127	1,138 (15.3%)	418 (14.9%)	0.062	819 (20.4%)	324 (18.2%)	0.025	605 (28.4%)	265 (23.9%)	0.003
Trunk	1,851 (37.4%)	893 (39.9%)		2,481 (33.4%)	1,007 (35.9%)		1,154 (28.8%)	568 (31.9%)		628 (29.5%)	383 (34.5%)	
Extremities	2,385 (48.2%)	1,036 (46.3%)		3,803 (51.2%)	1,380 (49.2%)		2,037 (50.8%)	887 (49.9%)		898 (42.1%)	463 (41.7%)	
Ulceration												
No	4,515 (91.3%)	2,029 (90.7%)	0.454	6,066 (81.7%)	2,259 (80.5%)	0.166	2,412 (60.1%)	1,046 (58.8%)	0.333	991 (46.5%)	498 (44.8%)	0.362
Yes	431 (8.7%)	207 (9.3%)		1,356 (18.3%)	546 (19.5%)		1,598 (39.9%)	733 (41.2%)		1,140 (53.5%)	613 (55.2%)	
Facility type												
Non-academic/research program	3,034 (61.3%)	1,325 (59.3%)	0.094	3,494 (47.1%)	1,614 (57.5%)	<0.001	2,254 (56.2%)	781 (43.9%)	<0.001	935 (43.9%)	592 (53.3%)	<0.001
Academic/research program	1,912 (38.7%)	911 (40.7%)		3,928 (52.9%)	1,191 (42.5%)		1,756 (43.8%)	998 (56.1%)		1,196 (56.1%)	519 (46.7%)	

NOS: Not otherwise specified.

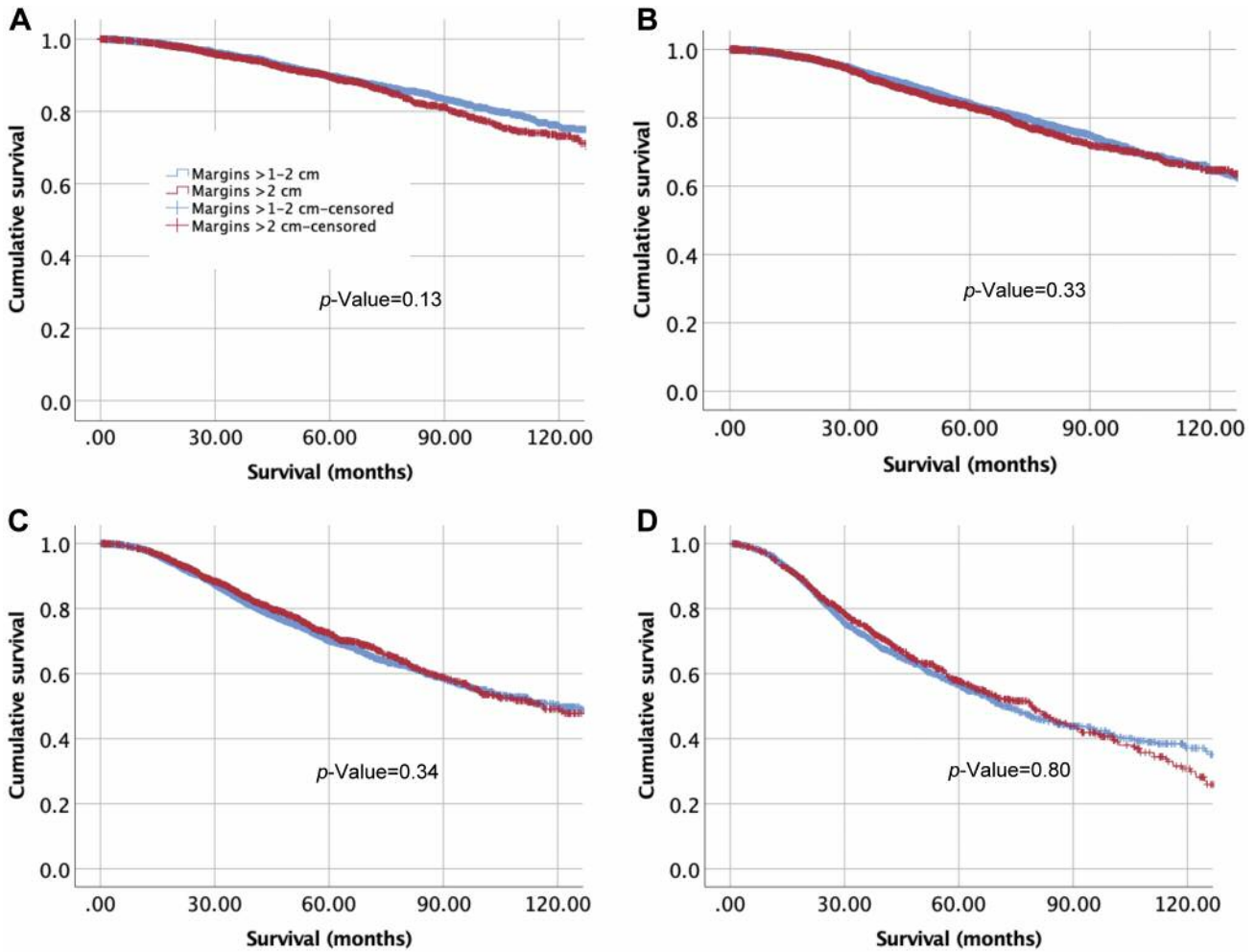


Figure 1. Ten-year overall survival according to excisional margins for patients with melanoma of Breslow depth ≤ 1 mm (A), 1.01-2 mm (B), 2.01-4 mm (C) and > 4 mm (D).

Table II. Multivariable logistic regression models for each Breslow group looking at factors associated with excisional margins > 2 cm.

Variable	Breslow depth							
	≤ 1.00 mm		1.01-2.00 mm		2.01-4.00 mm		> 4.00 mm	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Female	1.09 (0.98-1.21)	0.13	1.01 (0.91-1.10)	0.93	0.92 (0.81-1.04)	0.16	0.94 (0.80-1.10)	0.43
61-80 Years	1.10 (0.99-1.23)	0.07	1.01 (0.92-1.11)	0.85	0.85 (0.76-0.97)	0.02	0.99 (0.84-1.17)	0.92
> 80 years	1.01 (0.81-1.27)	0.91	1.04 (0.88-1.24)	0.62	0.91 (0.76-1.10)	0.33	0.95 (0.76-1.18)	0.64
Comorbidities	1.10 (0.95-1.28)	0.20	1.00 (0.88-1.13)	0.99	1.10 (0.95-1.27)	0.21	1.06 (0.88-1.27)	0.55
Head and neck, skin NOS, overlapping lesion	0.99 (0.85-1.17)	0.95	1.03 (0.91-1.18)	0.62	0.93 (0.79-1.08)	0.32	0.86 (0.71-1.04)	0.11
Trunk	1.14 (1.02-1.28)	0.02	1.13 (1.02-1.25)	0.02	1.11 (0.97-1.26)	0.14	1.17 (0.98-1.39)	0.08
Ulceration present	1.06 (0.89-1.27)	0.50	1.08 (0.97-1.21)	0.16	1.07 (0.95-1.19)	0.28	1.04 (0.90-1.20)	0.63
Academic/research program	1.10 (0.99-1.22)	0.07	0.66 (0.60-0.72)	< 0.001	0.61 (0.55-0.69)	< 0.001	0.70 (0.60-0.81)	< 0.001

CI: Confidence interval; OR: odds ratio; NOS: not otherwise specified.

TNM classification, although the sample of patients decreased considerably. In addition, the two excisional margin groups in our study did not include that recommended by the NCCN for melanomas with Breslow depths of 1 mm or less (1 cm); therefore, we could not compare factors and survival between the recommended and wider margins. Nevertheless, we did find interesting results in patients with wider excisional margins (>1 cm) in this Breslow depth group. In conclusion, we found that location in the trunk increased the likelihood of wider than recommended excisional radial margins, while physicians that treat patients with invasive melanoma in academic/research facilities were more likely to follow the guidelines. Finally, differences in 10-year OS by excisional margins for all Breslow depth groups were not statistically significant.

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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