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ORIGINAL ARTICLE – MELANOMAS

Is a Wider Margin (2 cm vs. 1 cm) for a 1.01–2.0 mm Melanoma Necessary?

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ABSTRACT

Background. The current NCCN recommendation for resection margins in patients with melanomas between 1.01 and 2 mm deep is a 1–2 cm radial margin. We sought to determine whether margin width had an impact on local recurrence (LR), disease-specific survival (DSS), and type of wound closure.

Methods. Melanomas measuring 1.01–2.0 mm were evaluated at a single institution between 2008 and 2013. All patients had a 1 or 2 cm margin.

Results. We identified 965 patients who had a 1 cm (n = 302, 31.3 %) or 2 cm margin (n = 663, 68.7 %). Median age was 64 years, and 592 (61.3 %) were male; 32.5 and 48.7 % of head and neck and extremity patients had a 1 cm margin versus 18.9 % of trunk patients ($p < 0.001$). LR was 2.0 and 2.1 % for a 1 and 2 cm margin, respectively (p = not significant). Five-year DSS was 87 % for a 1 cm margin and 85 % for a 2 cm margin (p = not significant). Breslow thickness, melanoma on the head and neck, lymphovascular invasion, and sentinel lymph node biopsy (SLNB) status significantly predicted LR on univariate analysis; however, only location and SLNB status were associated with LR on multivariate analysis. Margin width was not significant for LR or DSS. Wider margins were associated with more frequent graft or flap use only on the head and neck ($p = 0.025$).

Conclusions. Our data show that selectively using a narrower margin of 1 cm did not increase the risk of LR or decrease DSS. Avoiding a 2 cm margin may decrease the need for graft/flap use on the head and neck.

The incidence of melanoma in the United States continues to increase with an estimated annual percentage increase ranging from 1.5 to 4.1 % in 2015.[1] Newer modalities of treatment for advanced metastatic disease, including immunotherapy and targeted therapies, have been introduced, whereas the surgical treatment of melanoma has undergone minimal change. The "gold standard" of treatment for localized melanoma is wide excision (WE) of the lesion with a 1 or 2 cm radial margin based on the thickness of melanoma. Several large, prospective trials have studied resection margins in melanomas ranging from 0.8 to 4 mm in thickness (summarized in Table 1).[2–7] These studies were unable to demonstrate a significant difference in overall survival (OS), disease-specific survival (DSS), or local recurrence (LR) when a wide margin of 4 or 5 cm was compared to narrow margin of 2 cm.[8] One of the earliest studies to report on margins of resection and recurrence was done by Veronesi et al. The authors showed a higher rate of recurrence when a 1 cm margin was used compared with a 3 cm margin for melanomas <2 mm in thickness, although this was not statistically significant. In addition, they reported no difference in OS.[9] The data produced from the aforementioned studies helped form the foundation for the National Comprehensive Cancer Network (NCCN) recommendations for a 1.01–2 mm melanoma.[10]

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TABLE 1 Summary of clinical studies assessing Breslow thickness and resection margin width

Study	Year	No. of patients	Breslow thickness (mm)	Margin width (cm)	Median follow-up (mo)	Local recurrence rate	5-year OS
Prospective studies							
Cascinelli	1998	612	<2	1 versus 3	90	No difference	No difference[a]
Cohn-Cedermark et al.	2000	989	0.8–2	2 versus 5	132	No difference	No difference
Balch et al.	2001	740	1–4	2 versus 4	120	No difference	No difference
Khayat et al.	2003	337	<2.1	2 versus 5	192	No difference	No difference
Thomas et al.	2004	774	≥3	1 versus 3	60	No difference[b]	No difference
Gillgren et al.	2011	936	>2	2 versus 4	80.4	No difference	No difference
Retrospective studies							
Hudson et al.	2012	576	1–2	1 versus 2	38	Increased with 1 cm margins[c]	No difference
Doepker et al.	2015	1024	1–2	1 versus 2	14.8	No difference	No difference

OS overall survival

[a] No statistical difference was seen in OS up to 12 years

[b] Statistical difference was seen in locoregional recurrence between the 1- and 3 cm margin groups

[c] Local recurrence was 3.6 and 0.9 % in the 1- and 2 cm margin groups, respectively ($p = 0.04$). This difference was seen on univariate analysis

Currently, the NCCN guidelines recommend either a 1 or 2 cm margin width based on evidence extrapolated from the trials summarized in Table 1. No prospective trial has directly compared a 1 or 2 cm margin width for a 1.01–2 mm melanoma. Typically, a surgeon will use their best discretion in choosing margin widths when treating melanomas 1.01–2 mm in thickness. Best discretion refers to the surgeon using a narrow margin to preserve functionality and cosmesis or to avoid a potential need for skin graft or flap reconstruction. A more recent single-center, retrospective series directly compared outcomes for a 1 to 2 mm melanoma using a 1 or 2 cm margin width.[11] Hudson et al. retrospectively reviewed 576 patients with 224 (38.9 %) having a 1 cm margin and 352 (61.1 %) having a 2 cm margin width. The distribution of LR was significant between the two groups; the 1 cm group had a recurrence rate of 3.6 % compared with only 0.9 % in the 2 cm group ($p = 0.044$). Interestingly, only head and neck location was associated with LR on multivariate analysis (MVA). The authors demonstrated no difference in OS between the two margin groups on MVA.[11]

We sought to add to the literature by directly comparing the use of a 1 or 2 cm margin width of resection for a 1.01- to 2 mm melanoma in a large, single institution, retrospective study. The goal of the study was to determine whether using a narrow margin had an impact on the need for a skin graft or flap reconstruction, local recurrence, or DSS in patients diagnosed with melanomas 1.01–2 mm in thickness.

METHODS

After obtaining Institutional Review Board approval, a retrospective series of consecutive patients diagnosed with melanoma 1.01–2 mm was identified from a single-institution database of patients from 2002 to 2013. All patients had a WE with a 1 or 2 cm radial margin from the clinically visible edge of any remaining pigmented lesion or biopsy scar. Demographic and clinicopathologic characteristics (sex, age at diagnosis, histologic subtype, location of primary tumor, Breslow thickness, and sentinel lymph node biopsy (SLNB) status) along with outcomes data were retrieved. Ulceration, lymphovascular invasion (LVI), and mitotic rate (MR) also were evaluated, although these features were not uniformly recorded for all patients on final pathology (Table 2). Satellitosis, vertical growth phase, and regression were not included in the final analysis due to the high number of unavailable data points. Patients who had reexcision for melanoma in situ or residual disease at the margins after undergoing a 1 or 2 cm margin were also excluded.

All cases were reviewed and confirmed by a board-certified dermatopathologist. All available original tissue biopsies performed at an outside institution were reexamined before clinical evaluation or surgery. Not all patients had SLNB, which was due to patient preference, comorbid conditions preventing the use of general anesthesia, or failure to map on preoperative lymphosctinigraphy. All patients with SLN metastases were offered completion lymph node dissection (CLND) as standard of care. Recurrence during follow-up was categorized as local, regional nodal/in-transit, or distant. LR was defined as recurrence within 2 cm of the scar or graft.

Statistical Analysis

Chi square tests were performed on categorical variables. Wilcoxon rank-sum tests or analysis of variance tests were used for continuous variables to test for differences between

TABLE 2 Patient demographics and tumor characteristics stratified by resection margin

Variable	All patients $N = 965$	1 cm $n = 302$ (31.3 %)	2 cm $n = 663$ (68.7 %)	p value
Gender (%)				
Male	592 (61.3)	177 (58.6)	415 (62.6)	0.263
Female	373 (38.7)	125 (41.4)	248 (37.4)	
Age (years)				
Median (range)	64 (15–96)	67 (15–96)	63 (15–90)	**0.004**
Histologic type (%)[a]				
Superficial spreading	562 (58.2)	182 (60.3)	380 (57.3)	**0.017**
Nodular	218 (22.6)	52 (17.2)	166 (25)	
Acral lentiginous	22 (2.3)	12 (4.0)	10 (1.5)	
Lentigo maligna	44 (4.6)	21 (7.0)	23 (3.5)	
Pure desmoplastic	14 (1.5)	5 (1.7)	9 (1.4)	
Mixed desmoplastic	8 (0.8)	2 (0.7)	6 (0.9)	
Desmoplastic (NOS)	2 (0.2)	1 (0.3)	1 (0.2)	
Other	18 (1.9)	5 (1.7)	13 (2.0)	
Location of primary (%)				
Head/neck	195 (20.2)	98 (32.5)	97 (14.6)	**<0.001**
Trunk	330 (34.2)	57 (18.9)	273 (41.2)	
Extremities				
UE	275 (28.5)	93 (30.8)	182 (27.5)	
LE	165 (17.1)	54 (17.9)	111 (16.7)	
Breslow thickness (mm)				
Median	1.4	1.3	1.4	**<0.001**
Ulceration (%)[a]				
Present	195 (20.2)	64 (21.2)	131 (19.8)	0.679
Absent	750 (77.7)	234 (77.5)	516 (77.8)	
LVI (%)[a]				
Present	18 (1.9)	3 (1.0)	15 (2.3)	0.225
Absent	907 (94)	289 (95.7)	618 (93.2)	
MR (%)[a]				
<1 mm^2	253 (26.2)	75 (24.8)	178 (26.8)	0.157
1–2 mm^2	375 (38.9)	133 (44)	242 (36.5)	
>2 mm^2	308 (31.9)	90 (29.8)	218 (32.9)	
SLNB pathology (%)[b]				
Negative	751 (77.8)	214 (70.9)	537 (81.0)	0.190
Positive	114 (11.8)	25 (8.3)	89 (13.4)	

Bold values indicate statistically significant

LVI lymphovascular invasion; *MR* mitotic rate; *SLNB* sentinel lymph node biopsy; *NOS* not otherwise specified; *LE* lower extremity; *US* ultrasound

[a] Data unavailable or missing for histologic subtype in 77 cases, for ulceration in 20 cases, for LVI in 40 cases, and for mitotic rate in 29 cases; unavailable or missing data have been removed prior to testing

[b] SLNB was not performed in 100 patients

1 and 2 cm margins of resection. Five-year OS and DSS rates were calculated using the Kaplan–Meier (KM) method of estimation. Survival curves were compared with the log-rank test. Statistical significance was determined by a p value of <0.05. Hazard ratios were estimated by Cox proportional hazards model. All analysis was done in R, version 3.1.0 (a statistical computing environment).

RESULTS

Patient Characteristics

A total of 965 patients met study criteria and were included for review and analysis. The median age of the cohort was 64 (range 15–96) years, and 592 (61.3 %) were

male. The median Breslow thickness for the entire cohort was 1.4 mm. The predominant histologic subtype was superficial spreading in 562 (58.2 %). Of the 965, 302 (31.3 %) had a 1 cm margin and 663 (68.7 %) had a 2 cm margin (Table 2). One-centimeter margins were more frequently employed for extremity and head and neck locations compared with the trunk. Of the 302 who had a 1 cm margin, 245 (81.1 %) were located on the extremities and head and neck compared with 57 (18.9 %) on the trunk; however, 41.2 % of those with truncal melanomas had 2 cm margins ($p < 0.001$). No difference was seen in the histologic prognostic parameters between the two margin groups (Table 2).

Wound Closure

Patients included in our study had their wounds closed primarily, with a split-thickness skin graft (STSG), full-thickness skin graft (FTSG), or flap reconstruction. The rate of primary closure and skin graft or flap reconstruction between the two margin groups is shown in Table 3. Of the 965 patients, 660 (68.4 %) were closed primarily, whereas 305 (31.6 %) had either a skin graft or flap reconstruction. Primary closure was most frequent in truncal melanomas (88.2 %) (Table 3). Of the 965 patients, 94 had both a 1 cm margin and a skin graft or flap/graft closure. Of those 94, 67 patients (71.3 %) had a primary lesion located on the nose, near the eye or temple. Ninety-seven of 195 (49.7 %) patients with head and neck melanomas had a 2 cm margin; 80 (82.5 %) of those needed a skin graft or flap for closure ($p = 0.025$). Of the 440 with extremity lesions, 293 (67.9 %) had a 2 cm margin, and of those, 94 (32.1 %) needed a graft or flap reconstruction compared with 25 (17.0 %) with 1 cm margins.

Recurrence

The median follow-up of the entire cohort was 15 (range 0.2–129) months. Of the 965 patients, 20 (2.1 %) experienced local recurrence, and of those, 6 (2.0 %) experienced a LR with a 1 cm margin and 14 (2.1 %) with a 2 cm margin, respectively ($p = 0.791$; Table 4). There was no statistical difference in LR between the margin widths. On univariate analysis (UVA), Breslow thickness, LVI, melanoma on the head and neck, and a positive SLNB were significant for local recurrence. However, only head and neck location ($p = 0.004$) and SLNB ($p < 0.001$) retained significance on MVA (Table 5). Margin width demonstrated no impact on local recurrence, regional nodal/in-transit, or distant recurrence on either UVA or MVA.

Survival Analysis

At the time of last follow-up, 862 (89.3 %) patients were alive (829 were alive without evidence of melanoma and 33 with evidence of recurrent melanoma). Overall, 103 (10.7 %) patients died. Of those, 41 (39.8 %) died of disease and the remaining 62 (60.2 %) died of unknown or other causes. Of those who had a 1 or a 2 cm margin of resection, 38 (12.6 %) and 65 patients (9.8 %) died, respectively. Ten patients (3.3 %) with a 1 cm margin and 31 patients (4.7 %) with a 2 cm margin died of melanoma. The median OS for the entire cohort was 92.2 months, whereas the median DSS was not reached. The 5-year OS and DSS for the entire cohort were 69.3 and 84.7 %, respectively (Fig. 1).

TABLE 3 Distribution of wound closure

	All patients $N = 965$	1 cm $n = 302$	2 cm $n = 663$	p value
Wound closure by margin (%)				
Primary	660 (68.4)	208 (68.9)	452 (68.2)	0.885
Skin graft/flap	305 (31.6)	94 (31.1)	211 (31.8)	
Wound closure by location (%)				
Head/neck	195	98	97	**0.025**
Primary	48 (24.6)	31 (31.6)	17 (17.5)	
Skin graft/flap	147 (75.4)	67 (68.4)	80 (82.5)	
Trunk	330	57	273	0.056
Primary	291 (88.2)	55 (96.5)	236 (86.4)	
Skin graft/flap	39 (11.8)	2 (3.5)	37 (13.6)	
Extremities	440	147	293	**0.001**
Primary	321 (73.0)	122 (83.0)	199 (67.9)	
Skin graft/flap	119 (27.0)	25 (17.0)	94 (32.1)	

Bold values indicate statistically significant

TABLE 4 Patterns of recurrence

Recurrence (%)[a]	All recurrences $N = 105$	1 cm $n = 29$	2 cm $n = 76$	p value
Local	20 (2.1)	6 (2.0)	14 (2.1)	0.791
Regional nodal/in-transit	44 (4.6)	12 (4.0)	32 (4.8)	0.946
Distant	41 (4.2)	11 (3.6)	30 (4.5)	0.885

[a] Percentages are out of all patients having that excision margin

TABLE 5 Univariate and multivariate analysis of predictive factors for local recurrence

Variable	Local Recurrence			
	Univariate		Multivariate	
	Odds ratio (95 % CI)	p value	Odds ratio (95 % CI)	p value
Breslow thickness	4.01 (1.01–15.91)	**0.048**	3.23 (0.64–16.14)	0.154
Ulceration	1.40 (0.50–3.91)	0.519	1.16 (0.39–3.47)	0.786
LVI	7.98 (1.66–38.44)	**0.010**	3.71 (0.65–21.32)	0.142
Head and neck location	2.83 (1.14–7.03)	**0.025**	4.68 (1.62–13.51)	**0.004**
Margin width	1.09 (0.41–2.85)	0.868	1.02 (0.34–3.04)	0.971
SLNB status	7.30 (2.93–18.16)	**<0.001**	8.26 (3.05–22.37)	**<0.001**

Bold values indicate statistically significant

SLNB sentinel lymph node biopsy; *LVI* lymphovascular invasion; *CI* confidence interval

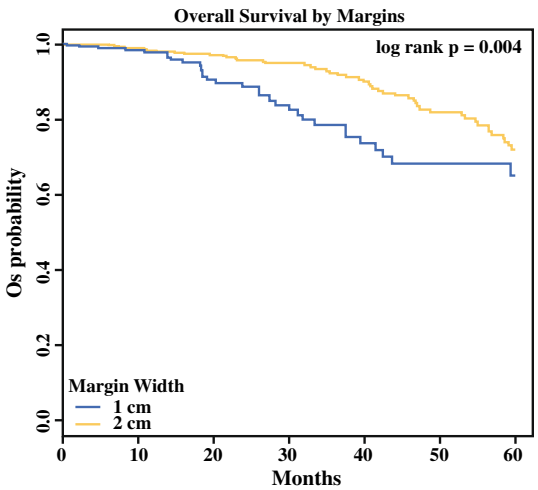

FIG. 1 Overall survival (OS). Kaplan–Meier estimates of OS by margins of resection (2 vs. 1 cm). A significant difference was seen between the different margins

Overall Survival

The 5-year OS for a 1- and 2 cm margin was 61.9 and 71.2 % [hazard ratio (HR) = 0.52, 95 % confidence interval (CI) 0.35–0.78, $p = 0.004$], as demonstrated by KM survival analysis (Fig. 1). Margin width, ulceration, age, and sex were found to be significant predictors of OS on UVA. Margin width (HR = 0.66, 95 % CI 0.43–1.04, $p = 0.050$), ulceration (HR = 1.67, 95 % CI 1.08–2.58, $p = 0.021$), and age (HR = 1.03, 95 % CI 1.00–1.04, $p = 0.002$) remained significant predictors of OS on MVA.

Disease-specific Survival

The 5-year DSS between the two margin groups was not statistically different (1 cm 87 %, 2 cm 85 %, $p = 0.758$; Fig. 2). On UVA, Breslow thickness, ulceration, LVI, and increased MR (>2/mm^2) were statistically significant predictors of DSS. However, only LVI (HR = 3.14, 95 % CI 1.25–7.88, $p = 0.010$) retained significance on MVA. The KM curve demonstrated overlapping curves for both margin groups with a median follow-up of 15 months.

DISCUSSION

The effect of margin width on recurrence and survival with a melanoma (1–4 mm) has been well studied and documented in the literature. A recent meta-analysis by Lens et al. pooled and analyzed data from five prospective trials, which looked at wide versus narrow margins in melanomas ranging in thickness from 1 to 4 mm. The authors concluded there was no statistical difference in LR or overall mortality.[12] The limitations of this study are the inherent flaws seen with a meta-analysis, which included clinical heterogeneity associated with varied follow-up periods, different methods for determining local recurrence, and varying thicknesses. Even though there are discrepancies between those studies, the NCCN has used

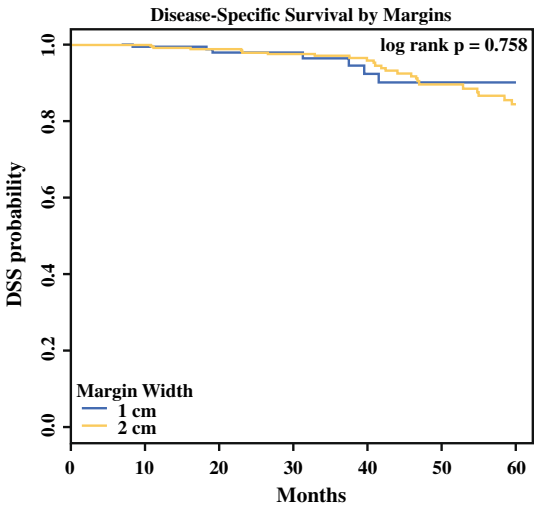

FIG. 2 Disease-specific survival (DSS). Kaplan–Meier estimates of DSS by margins of resection (2 vs. 1 cm). No significant difference was seen between the different margins. Median survival was not reached

the data to create guidelines for the recommended excision width of melanoma from 1 to 4 mm.[10] A randomized, prospective trial comparing a 1 or 2 cm margin width for 1.01–2 mm is lacking. Several smaller, nonrandomized, retrospective trials have tried to answer the question of which margin is optimal and how it will affect recurrence and survival. We analyzed our extensive database and sought to determine whether margin width truly had an impact on local recurrence, DSS, and wound closure.

The LR rate in our study was not shown to differ significantly between the two margin widths ($p = 0.791$). We evaluated other factors and found head and neck location, SLNB status, and LVI to be significant on UVA. When included in the MVA, only head and neck location and SLNB status retained significance for local recurrence, a finding similar to one published by Hudson et al.[11] The LR rate was the same between both margin groups in this study. In the current study, the surgeons used their best judgment and may have performed a wider margin for lesions with aggressive features, such as ulceration or LVI. When looking at our data more closely, we found that patients with LVI have a higher rate of LR with a 2 cm margin width compared with a 1 cm margin width ($p = 0.010$). When we evaluated other aggressive biologic features, such as ulceration, MR, and satellitosis, there was no difference between the groups. Based on this, we are unable to state conclusively that if a lesion has these specific aggressive features then a wider margin should be utilized, although a surgeon may choose to proceed with a wider margin based on personal preference in their practice.

According to the 7th edition of the AJCC staging system and the Intergroup Trial, ulceration and head and neck location were associated with worse OS.[4,13] Margin width, ulceration, and age were significant predictors of OS on MVA in our study; however, ulceration was only significant on UVA for DSS. Despite a difference seen in OS between the groups, our study demonstrated no difference in DSS when accounting for margin width or location. These conclusions may become very important when the surgeon is trying to decide whether to preserve cosmesis and functionality by avoiding a wider margin, especially on the head or neck or distal extremity.

If there is a choice to perform a narrow margin and avoid a potential skin graft or flap reconstruction, the surgeon will likely gravitate to that option. The use of skin grafts or flap reconstruction can be cosmetically unappealing and potentially increase the cost of care and the overall morbidity for the patient.[14,15] Our study is the first to compare directly the use of skin grafts and flap reconstruction versus primary closure in those receiving a 1- or 2 cm margin width. The majority of wounds were closed primarily, but our study does indicate that surgeons favored using a narrow margin in areas where a skin graft or flap reconstruction would likely be needed if a wider margin was used, such as the head and neck or extremity. Avoiding a 2 cm margin may decrease the need for a skin graft or flap, especially areas where functionality and cosmesis are more important, such as the head and neck. We recognize that this conclusion is drawn from a retrospective analysis, and a larger, prospective trial will be needed to answer this question accurately.

Some of the recognized limitations in our study are derived from the inherent flaws of a retrospective study with missing data points for some patients and selection bias. One limitation in this study is the short median follow-up seen with our patients. Most local recurrences occur within the first 2 years.[7] After 2 years of established follow-up in the surgical clinic, the lower risk patients might be discharged and referred back to their local dermatologist. The dermatologist is informed to contact the clinic if there were any signs of recurrence. However, with that being said longer median follow-ups of 38 and 46 months have been reported in the literature with no difference being seen with OS, DSS, or LR.[11,15]

CONCLUSIONS

In our experience, utilizing a narrow margin of 1 cm did not increase the risk of LR in our patient population. We demonstrated no difference in DSS between the two margin widths. If surgeons are able to avoid a wider margin of 2 cm, they may be able to reduce the need for use of a graft or flap reconstruction on the head and neck or extremity without potentially increasing the chance of a recurrence or

decreasing survival. There is currently a multinational, multicenter, prospective, randomized control trial (MelmarT) comparing 1- versus 2 cm margins of excision in patients with $\geq$1 mm melanomas with an estimated completion date of December 2029.[16] The primary outcome of the trial will evaluate LR and melanoma-specific survival.

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