Local Recurrence and Survival in Patients With Melanoma >2 mm in Thickness at Difficult Sites Treated With 1-cm Versus 2-cm Margins

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Abstract

Background: Melanoma guidelines recommend surgical excision with 2-cm margins for melanomas >2 mm in thickness. However, this procedure may be problematic at critical anatomic sites. We aimed to compare the outcomes of wide (2 cm) versus narrow (1 cm) excision margins in patients with melanoma >2 mm in thickness near critical structures. **Patients and Methods:** We retrospectively examined 736 patients undergoing excision with wide versus narrow margins at the National Cancer Institute in Milan, Italy, between 2001 and 2015. **Results:** A total of 265 (36.0%) patients received a wide local excision—82 (30.9%) with linear repair and 183 (69.1%) with flap or graft reconstruction. A total of 471 (64.0%) patients received a narrow excision—320 (67.9%) with linear repair and 151 (32.1%) with flap or graft reconstruction ($P<.001$). The 10-year overall survival rate was 69.5% (95% CI, 63.3%–76.2%) in the wide group and 68.7% (95% CI, 63.8%–74.0%) in the narrow group ($P=.462$); 10-year crude cumulative incidence (CCI) of local recurrence was 5.4% (95% CI, 3.2%–9.2%) in the wide and 8.8% (95% CI, 6.4%–12.1%) in the narrow group ($P=.150$). Multivariable Fine-Gray modeling of the CCI of local recurrence showed that Breslow thickness ($P=.010$) was the only statistically significant parameter. Multivariable Cox models for overall survival showed that age ($P<.001$), Breslow thickness ($P<.001$), and sentinel lymph node status ($P=.019$) were statistically significant covariates. Excision margin was not a significant parameter affecting patients' outcome. **Conclusions:** Wide local excision with 1-cm margins for melanoma >2 mm in thickness was not associated with an increased risk of local recurrence and did not affect overall survival.

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Background

Surgical excision according to Breslow thickness is the mainstay of treatment of primary cutaneous melanoma.[1–4] Postoperative complications can be contained using a conservative approach with narrower surgical margins. The risk of recurrence after a reduced margin is balanced by the higher risk of morbidities associated with a wider excision.

However, despite specific randomized trials, the issue of optimal surgical excision margins remains controversial in melanoma management, and it is still unclear how the surgical clearance margins after the removal of a primary melanoma may affect metastatic spread.[5–9] The results of some studies[6,9] did not show a significant differential risk for melanoma-specific survival (MSS) associated with different surgical clearance margins, whereas other analyses showed that narrow excisions negatively affected MSS.[5,7,8]

Current melanoma guidelines[1–4] recommend 1- to 2-cm excision margins based on the Breslow thickness of the primary tumor, but give different indications regarding the width of surgical excision for lesions >2 mm. The guidelines recommend wide local excision (WLE) to eradicate microsatellites around the primary site and decrease the risk of locoregional recurrence and a poor outcome. However, although microsatellites reflect an aggressive tumor biology associated with a higher incidence of regional lymph node metastases as well as worse disease-free survival (DFS) and overall survival (OS), they are present only in a small percentage (4%–8%) of melanomas.[10–12] Furthermore, in recent years, melanoma treatment has rapidly evolved with the availability of effective systemic therapies (immune checkpoint inhibition and targeted therapies), improving outcome in adjuvant[13–16] and metastatic settings.[17–20] In such a new context, patients with microsatellites (stage IIIB–C) and also those with high-risk stage II melanoma (stage IIB–C) are eligible for adjuvant therapy.[21,22] It could therefore be hypothesized that WLE, often associated with reconstructive surgery, could be avoided in a substantial proportion of patients with melanoma,[23] and high-risk patients could be effectively treated with adjuvant therapy.[21,22] Another issue to consider in clinical decision-making is the critical location of primary melanomas, often on the scalp or face (forehead, cheeks, ears, lips, nose, eyelids), where reducing the safety margins using a more conservative approach to avoid cosmetic problems and/or functional compromise could increase the risk of local recurrence or death.

Recognizing these issues may prompt further investigations to offer better answers and perhaps allow true personalization of surgical recommendations. The primary aim of the present study was to investigate whether a narrower (1-cm) WLE was safe in patients with a primary melanoma >2 mm in thickness at sites

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close to critical structures. The secondary aim was to compare the need for reconstructive surgery in different patient groups. We retrospectively assessed patients undergoing standard WLE and those who declined a 2-cm margin in favor of a 1-cm WLE, and compared outcomes in these 2 groups.

Patients and Methods

A total of 831 consecutive patients aged ≥18 years diagnosed with primary localized cutaneous melanoma >2 mm thick on either the head/face, acral areas (sole of foot, palm of hand, digital and interdigital areas), external genitalia, or periumbilical and perineal areas, consecutively treated between 2001 and 2015 at the National Cancer Institute in Milan, Italy, were considered for study inclusion. A total of 60 (7.2%) patients with missing data, 14 (1.7%) with a history of other invasive cancer (other than basal cell carcinoma), and 5 (0.6%) with primary mucosal melanomas were excluded. An additional 16 (1.9%) patients were excluded because they had incomplete excision margins after WLE (including cases with melanocytic atypia at resection margins). Thus, the final cohort included 736 patients.

The following data were retrieved from prospectively maintained databases: sex, age, site of primary tumor (ie, head/face, genital/umbilical/perineal area, acral area), melanoma subtype (acral lentiginous melanoma [ALM], desmoplastic melanoma [DM], nodular melanoma [NM], superficial spreading melanoma [SSM]), Breslow thickness, ulceration, mitotic rate (MR)/mm^2, Clark level, microsatellites, and sentinel lymph node (SLN) status. All slides were reviewed by dermatopathologists according to a common protocol.[24] Stages of all cases were revised according to the 8th edition of the AJCC Cancer Staging Manual.[25]

Surgical treatments were performed after obtaining each patient's written informed consent. Patients underwent an initial diagnostic excision. After histologic confirmation of melanoma >2 mm in thickness (stage T3–T4),[25] patients whose lesions arose at locations allowing the surgical procedure recommended by the then-current guidelines[2–4,26–29] and who accepted the procedure underwent WLE to achieve the recommended minimum margin of 2 cm, whereas patients who had comorbidities contraindicating the standard procedure[2–4,26–29] or whose lesions arose at locations where the standard procedure could not be applied, or who declined the standard procedure for cosmetic reasons, underwent WLE to achieve a total margin of 1 cm. The deep muscular fascia was always preserved.

Patients in whom the final WLE margin was 1 cm comprised the "narrow group" and those with a final margin of 2 cm the "wide group." All patients underwent SLN biopsy and those with a positive SLN underwent completion lymph node dissection. None of the patients received adjuvant therapy.

Statistical Methods

The primary aims of the study were to compare OS, DFS, and crude cumulative incidence (CCI) of local recurrence (LR) between the wide and narrow groups, assessed from the date of diagnosis. OS was defined as the time to death for any cause. DFS was defined as time to recurrence or death, whichever occurred first. CCI of LR was estimated in a competing risk setting, with regional relapse, distant relapse, and death considered as competing events. Times were censored at the latest follow-up for patients still alive and free from any relevant event. OS and DFS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. CCI curves were compared using the Gray test.

General and clinicopathologic differences between groups were assessed by the standardized mean difference (SMD).[30,31] As a measure of the magnitude of mean differences, SMD takes continuous values from 0 to infinity; the higher the SMD, the greater the difference. An SMD of around 0.3 is considered to indicate a possible between-group imbalance, although the clinical relevance of SMDs also needs to be assessed.

With regard to the secondary aim of our study—to compare the need for reconstructive surgery in the 2 groups—associations between the requirement for reconstruction and group characteristics were assessed using Fisher exact test. Associations between clinicopathologic characteristics including Breslow thickness, presence of ulceration, SLN status, age, tumor site, subtype, and outcomes were assessed using the Cox (OS, DFS) and Fine-Gray (CCI of LR, expressed as subdistribution hazard ratio) univariable and multivariable models.

Median follow-up was estimated from MSS data with the reverse Kaplan-Meier method.[32] Continuous variables were modeled using 3-knot restricted cubic splines to obtain a flexible fit.[33] The analyses were conducted using SAS 9.2 (SAS Institute Inc) and R software (R Foundation for Statistical Computing).

Results

Excision Margins and Patient and Tumor Characteristics

Of the 736 patients with >2-mm-thick melanomas, 265 (36%) underwent a WLE with 2-cm margins and 471 (64%) with 1-cm margins. Overall, 46.9% were female. The most common lesion site was the head/face (64.8%) and the most common melanoma subtype was SSM (48.4%), followed by NM (30.3%). The median (first and third quartiles) Breslow thickness was 3.5 mm (range, 2.6–5.0 mm) and the median MR was 5.0/mm^2 (range, 3.0–8.0/mm^2). Ulceration was present in 59.5% and SLN was positive in 41.0% of patients.

In the wide group, there was a male majority (63.0%; SMD, 0.315) and patients were older (61.2 vs 54.3 years; SMD, 0.546) than in the narrow group. Breslow thickness was similar between groups (3.6 vs 3.3 mm; SMD, 0.118). DM cases were more frequent in the wide group (8.7% vs 3.2%; SMD, 0.235), whereas the presence of microsatellites (6.8% vs 6.6%; SMD, 0.009) and SLN positivity (42.3% vs 40.3%; SMD, 0.039) was similar between groups. Characteristics of the 2 groups are summarized in Table 1.

Wound Closure and Reconstructive Surgery

In 112 of the 736 patients (15.2%), more than one re-excision was performed to achieve histopathologic clearance margins of 1 or 2 cm. The observed frequencies of re-excisions were 12.8% and 16.6% in the wide and narrow groups, respectively (SMD, 0.106). Re-excision numbers were similar between groups: 87 of 736 (11.8%) underwent 2 re-excisions—27 of 265 (10.2%) in the wide group and 60 of 471 (12.7%) in the narrow group—and 25 of 736 (3.4%) needed 3 re-excisions—7 of 265 (2.6%) in the wide group and 18 of 471 (3.8%) in the narrow group. The presence of microsatellites was significantly associated with re-excisions ($P<.001$).

Of the 265 patients in the wide group, 82 (30.9%) had linear repair and 183 (69.1%) required reconstruction with a skin graft or flaps. Of the 471 narrow-group patients, 320 (67.9%) had linear

Table 1. Clinicopathologic Characteristics of Patients With T3–T4 Melanomas at Difficult Sites

Characteristic	Overall n (%)	1-cm Margin n (%)	2-cm Margin n (%)	SMD
Total, N	736	471	265	
Sex				0.315
Female	345 (46.9)	247 (52.4)	98 (37.0)	
Male	391 (53.1)	224 (47.6)	167 (63.0)	
Age				0.546
Median (first and third quartiles), y	56.1 (47.8–65.7)	54.3 (46.2–62.3)	61.2 (51.8–68.1)	
Tumor site				0.053
Head/Face	477 (64.8)	307 (65.2)	170 (64.2)	
Genital/Periumbilical/Perineal area	46 (6.2)	31 (6.6)	15 (5.7)	
Acral areas	213 (28.9)	133 (28.2)	80 (30.2)	
Tumor subtype				0.235
Superficial spreading melanoma	356 (48.4)	234 (49.7)	122 (46.0)	
Nodular melanoma	223 (30.3)	144 (30.6)	79 (29.8)	
Acral lentiginous melanoma	119 (16.2)	78 (16.6)	41 (15.5)	
Desmoplastic melanoma	38 (5.2)	15 (3.2)	23 (8.7)	
Breslow thickness				0.118
Median (first and third quartiles), mm	3.5 (2.6–5.0)	3.3 (2.6–5.0)	3.6 (2.8–5.0)	
Ulceration				0.076
Absent	298 (40.5)	197 (41.8)	101 (38.1)	
Present	438 (59.5)	274 (58.2)	164 (61.9)	
Mitotic rate/mm^2				0.120
Median (first and third quartiles)	5.0 (3.0–8.0)	5.0 (3.0–7.0)	5.0 (3.0–8.0)	
Clark level				0.049
II–III	56 (7.6)	38 (8.1)	18 (6.8)	
IV–V	680 (92.4)	433 (91.9)	247 (93.2)	
Microsatellites				0.009
Absent	687 (93.3)	440 (93.4)	247 (93.2)	
Present	49 (6.7)	31 (6.6)	18 (6.8)	
Sentinel lymph node status				0.039
Negative	434 (59.0)	281 (59.7)	153 (57.7)	
Positive	302 (41.0)	190 (40.3)	112 (42.3)	

Abbreviation: SMD, standardized mean difference.

repair and 151 (32.1%) required a skin graft or flaps. The difference in reconstruction frequency between groups was significant (1 vs 2 cm: odds ratio, 0.28 [95% CI, 0.18–0.42]; $P<.001$). Clear lateral margins of 1 cm in the narrow group and 2 cm in the wide group, as well as clean deep margins with preservation of the deep muscular fascia, were histologically confirmed in all cases.

Local Recurrence and Survival

The overall median (first and third quartiles) follow-up was 108 months (57–124 months). After a median follow-up of 95 months (range, 51–123 months) and 114 months (range, 63–125 months) in the wide and narrow groups, respectively, 10-year OS was 69.5% (95% CI, 63.3%–76.2%) and 68.7% (95% CI, 63.8%–74.0%), respectively ($P=.462$); DFS was 63.4% (95% CI, 57.3%–70.2%) and 57.2% (95% CI, 52.2%–62.8%), respectively ($P=.246$); and CCI of LR was 5.4% (95% CI, 3.2%–9.2%) and 8.8% (95% CI, 6.4%–12.1%), respectively ($P=.150$) (Figure 1).

The incidence of LR according to melanoma subtype did not show significant differences overall or between study groups within each subtype group (data not shown).

Association Analyses

Results of the univariable and multivariable Fine-Gray models for CCI of LR are shown in Table 2. Both at univariable and multivariable analysis, only Breslow thickness was significantly associated with disease outcome. Excision margins did not prove to be significantly associated with outcome.

Results of the univariable and multivariable Cox models for OS are shown in Table 3. At univariable analysis, patient age, Breslow thickness, and SLN status were statistically significant covariates. At multivariable analysis, age, Breslow thickness, and SLN status remained the only statistically significant covariates.

Results of the univariable and multivariable Cox models for DFS are shown in Table 4. At univariable analysis, patient age, Breslow thickness, and SLN status were statistically significant covariates. Ulceration was an additional significant covariate in multivariable analysis.

Finally, the difference in reconstruction frequency between groups was highly significant ($P<.001$).

Discussion

Our main finding was that treating >2-mm-thick primary melanoma using WLE with 1-cm margins, rather than 2-cm margins as recommended by guidelines,[1–4] did not significantly affect CCI of LR or survival. In the multivariable models, we observed that age, Breslow thickness, ulceration, and SLN status had an impact on DFS probability. However, only age, Breslow thickness, and SLN status were statistically significantly associated with OS. It is also noteworthy that neither the excision margin

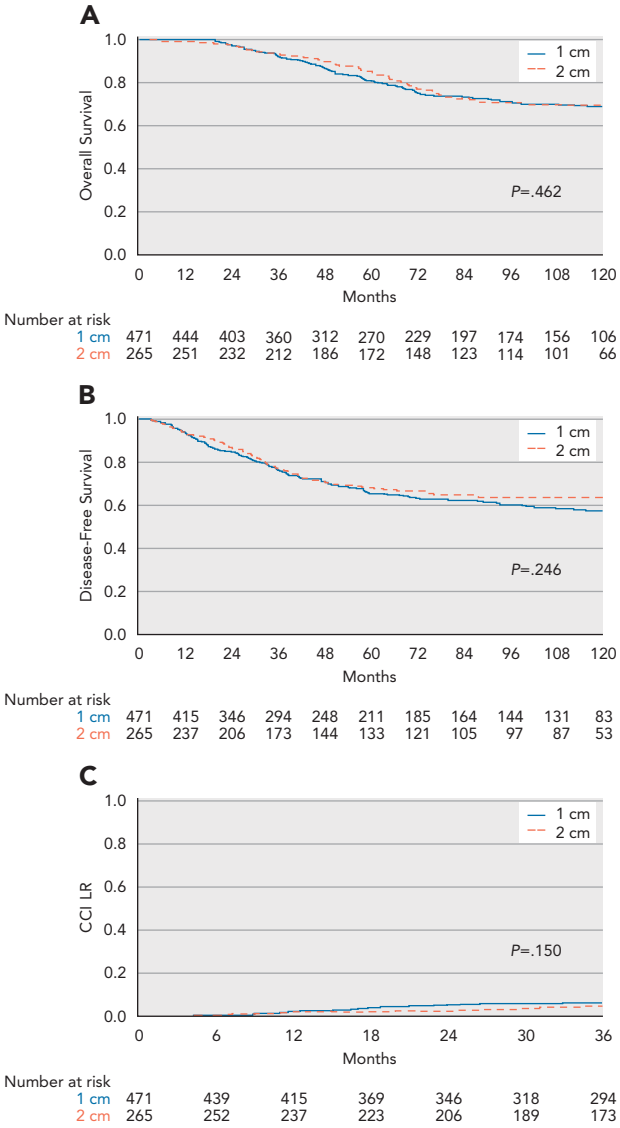

Figure 1. Kaplan-Meier curves of **(A)** overall survival, **(B)** disease-free survival, and **(C)** CCI of LR for patients with T3-T4 melanomas close to critical structures, according to excision margin width (2 cm vs 1 cm). Abbreviations: CCI, crude cumulative incidence; LR, local relapse.

nor the melanoma subtype showed a significant association with LR; Breslow thickness remained the only factor associated with LR in both univariable and multivariable analysis. The presence of microsatellites was significantly associated with re-excisions ($P<.001$), but this parameter only partially explains the observed re-excision incidence. The high frequency may also be due to the presence of cases of the DM subtype (n=38; 5.2%), for which clean margins are generally difficult to achieve.[34,35]

Earlier studies evaluating the impact of reduced resection margins in thick melanomas on LR and survival produced discordant results. Rawlani et al[36] retrospectively investigated a small cohort of 79 patients with head and neck melanomas close to the eye, nose, ear, and mouth treated with a reduced excision margin (1 cm) versus guideline-based WLE (2 cm) for melanomas ≥2 mm. They showed that reduced excision did not increase LR rates. Furthermore, after a follow-up of >5 years, the recurrence-free survival in patients undergoing reduced excision was 91.9%, compared with 90.4% in those undergoing guideline-based WLE. In a similar study, Hunger et al[37] retrospectively investigated a larger cohort of 325 patients undergoing tumor excision with 1-cm (n=228) or 2-cm (n=97) margins to evaluate differences in LR, locoregional spread, distant metastases, DFS, and OS. Their study did not show any significant differences in LR or disease outcome. Pasquali et al[38] investigated the impact of excision margins on locoregional disease control in patients with >4-mm-thick cutaneous melanomas and found that histopathologically determined excision margins >16 mm, corresponding to 2-cm surgical margins, were associated with better local control. Our findings confirmed the conclusions of Rawlani et al[36] and Hunger et al,[37] demonstrating that a narrow (1-cm) WLE did not significantly affect LR in patients with ≥2-mm-thick melanomas.

Regarding patient survival, a review by Hanna et al[39] on surgical excision margins in primary cutaneous melanoma did not show significant differences between narrow and wide margins in locoregional and distant recurrence or death due to melanoma. Their study also showed that wide margins (2–5 cm) increased the need for surgical reconstruction. In 2 separate analyses, Pandya et al[40] and Ruskin et al[41] retrospectively analyzed 2 series of 305 and 108 patients, respectively, surgically treated for primary melanomas on the head and neck, to identify potential differences in outcomes for patients who had reduced WLE margins. Their results showed that increasing margins did not improve patient outcome, with similar OS for all Breslow thicknesses treated with narrow WLE rather than the recommended WLE margins.[40,41]

Our study showed that in the multivariable model, age, Breslow thickness, ulceration, and SLN status were statistically significant covariates associated with DFS, whereas excision margins did not prove to be significantly associated with DFS. Furthermore, the results of the multivariable model for OS confirmed the results of previous studies,[39–41] showing that excision margin width was not a statistically significant factor affecting OS.

Given that Ruskin et al[41] stated that to date there have been no reported randomized trials including thick melanomas of the head and neck, this should be a consideration for future trial design. Results from the randomized trial by Hayes et al[8] suggested that 1-cm excision margins were inadequate for cutaneous melanoma with a Breslow thickness ≥2 mm on the trunk and limbs. However, there are important differences between this trial and our study.

One of the important differences is tumor site. The Hayes trial[8] included patients with one primary localized melanoma >2-mm in thickness arising on the trunk or limbs but not the palms of the hands and soles of the feet, whereas our study included patients with the same type of lesions on the head/face, acral areas, and other difficult locations. Furthermore, patients in the trial did not undergo SLN biopsy or elective lymph node dissection in case of SLN positivity, whereas all of our patients underwent SLN biopsy and those with a positive SLN underwent completion lymph node dissection. These procedural differences may have affected patients' outcomes significantly, particularly in terms of DFS and OS. Moreover, the prognostic importance of MR, lymphovascular invasion, and microsatellitosis was not known in the Hayes trial,[8] whereas these parameters were available and analyzed in our study.

In the Hayes trial,[8] patients were randomly assigned (1:1) to undergo resection with either a 1-cm or 3-cm excision margin following initial surgery. At the time of our study, the melanoma

Table 2. Fine-Gray Models for Crude Cumulative Incidence of Local Relapse

	Univariable		Multivariable	
	sHR (95% CI)	*P* Value	sHR (95% CI)	*P* Value
Age		.799		.563
65.7 vs 47.8 y	1.15 (0.76–1.74)		1.25 (0.83–1.88)	
Tumor site		.173		.189
Genital/Periumbilical/Perineal vs acral areas	2.36 (0.70–7.94)		2.57 (0.75–8.74)	
Head/Face vs acral areas	2.02 (0.94–4.34)		2.01 (0.90–4.49)	
Tumor subtype		.728		.852
DM vs ALM	1.05 (0.21–5.24)		1.12 (0.20–6.17)	
NM vs ALM	1.65 (0.65–4.20)		1.51 (0.57–3.98)	
SSM vs ALM	1.38 (0.73–0.59)		1.30 (0.52–3.29)	
Breslow thickness		.007		.010
5.0 vs 2.6[a] mm	2.25 (1.29–3.93)		2.36 (1.33–4.16)	
Ulceration		.830		.711
Present vs absent	1.06 (0.60–1.88)		0.89 (0.49–1.63)	
Width of excision margins		.150		.114
Wide vs narrow	0.63 (0.34–1.19)		0.59 (0.31–1.13)	
Sentinel lymph node status		.580		.901
Positive vs negative	1.17 (0.67–2.07)		0.96 (0.54–1.72)	

Abbreviations: ALM, acral lentiginous melanoma; DM, desmoplastic melanoma; NM, nodular melanoma; sHR, subdistribution hazard ratio; SSM, superficial spreading melanoma.
[a]Modeled as restricted cubic spline. Values represent the first and third quartiles.

guidelines recommended treating >2-mm-thick melanoma with a clearance margin of 2 cm.[26–29] Thus, we retrospectively evaluated patients with >2-mm-thick lesions at difficult sites who were treated with 1-cm versus 2-cm clearance margins. A further difference in the Hayes trial was that complete data were not available for all patients, whereas in our study complete clinicopathologic data of all patients were collected and available for analysis.

Moncrieff et al[42] demonstrated in a pilot study the feasibility of a randomized controlled trial (MelMarT) to provide a definitive answer to the optimal excision margin for patients with intermediate- to high-risk primary cutaneous melanoma. An ongoing randomized controlled trial, MelMarT-II, aims to determine the ideal margins for melanomas >2 mm and >1 mm with ulceration to limit the rate of LR.[43] This trial will randomize patients with clinical stage II melanoma into a 1-cm margin or 2-cm margin arm, with both arms undergoing SLN biopsies, and will follow the patients to determine safety and long-term outcomes.[43]

Regarding the secondary aim of our study, we found that fewer patients (32.1%) in the narrow group required reconstructive surgery than those in the wide group (69.1%). This difference was significant ($P<.001$) and suggests that narrower margins can reduce infection, poor healing, scarring, and mental issues often occurring with excisions close to critical structures. Rawlani et al[36] reported that in head and neck melanomas, especially lesions at critical sites such as the eyelid or nose, wide margins are

Table 3. Results of Univariable and Multivariable Cox Models for Overall Survival

	Univariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age		<.001		<.001
65.7 vs 47.8 y	4.45 (2.92–6.78)		1.70 (1.34–2.17)	
Tumor site		.928		.482
Genital/Periumbilical/Perineal vs acral areas	1.12 (0.60–2.10)		1.48 (0.78–2.81)	
Head/Face vs acral areas	1.00 (0.73–1.38)		1.07 (0.77–1.49)	
Tumor subtype		.981		.930
DM vs ALM	0.86 (0.41–1.81)		1.18 (0.55–2.56)	
NM vs ALM	1.00 (0.64–1.56)		0.94 (0.60–1.48)	
SSM vs ALM	0.98 (0.65–1.49)		1.01 (0.66–1.53)	
Breslow thickness		<.001		<.001
5.0 vs 2.6[a] mm	3.42 (2.35–4.99)		3.18 (2.16–4.67)	
Ulceration		.083		.298
Present vs absent	0.73 (0.54–0.98)		0.85 (0.62–1.16)	
Excision margin		.462		.395
Wide vs narrow	0.89 (0.66–1.21)		0.94 (0.77–1.38)	
Sentinel lymph node status		<.001		.019
Positive vs negative	0.59 (0.44–0.79)		0.70 (0.52–0.94)	

Abbreviations: ALM, acral lentiginous melanoma; DM, desmoplastic melanoma; HR, hazard ratio; NM, nodular melanoma; SSM, superficial spreading melanoma.
[a]Modeled as restricted cubic spline. Values represent the first and third quartiles.

Table 4. Results of Univariable and Multivariable Cox Models for Disease-Free Survival

	Univariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age		<.001		<.001
65.7 vs 47.8 y	4.08 (2.82–5.83)		1.70 (1.39–2.08)	
Tumor site		.797		.184
Genital/Periumbilical/Perineal vs acral areas	1.19 (0.70–2.02)		1.66 (0.97–2.85)	
Head/Face vs acral area	1.07 (0.80–1.41)		1.10 (0.82–1.46)	
Tumor subtype		.279		.372
DM vs ALM	0.88 (0.44–1.73)		1.05 (0.52–2.11)	
NM vs ALM	1.38 (0.93–2.05)		1.40 (0.94–2.08)	
SSM vs ALM	1.21 (0.83–1.75)		1.22 (0.84–1.78)	
Breslow thickness		<.001		<.001
5.0 vs 2.6[a] mm	2.98 (2.08–4.28)		3.99 (2.85–5.59)	
Ulceration		.246		.001
Present vs absent	0.86 (0.66–1.11)		0.63 (0.48–0.83)	
Excision margin		.226		.447
Wide vs narrow	0.85 (0.66–1.10)		1.11 (0.85–1.44)	
Sentinel lymph node status		<.001		.002
Positive vs negative	0.57 (0.45–0.74)		0.66 (0.51–0.86)	

Abbreviations: ALM, acral lentiginous melanoma; DM, desmoplastic melanoma; HR, hazard ratio; NM, nodular melanoma; SSM, superficial spreading melanoma.
[a]Modeled as restricted cubic spline. Values represent the first and third quartiles.

not always technically feasible or may lead to functional deformities. In addition, large defects often require soft tissue reconstruction with flaps, because they cannot be closed primarily.

The main strength of our study is that it comprised a large series with a long follow-up. Its limitations are that it was retrospective and that the wide and narrow groups were defined by patient decisions to accept or refuse the guideline recommendations. This could be a source of bias, particularly in terms of the strength of physician accounts of the possible aesthetic and functional sequelae of wide excision. Another limitation is that the histopathologic review was not centralized, although all slides were reviewed according to a common protocol.[24] Furthermore, our inclusion criteria were restricted and further studies are required before narrow margins can be adopted as a standard procedure for >2-mm-thick melanomas at other sites.

Conclusions

Our study showed that WLE with narrow (1-cm) margins for primary melanoma >2 mm in thickness occurring at critical sites was not associated with worse outcomes, but was associated with significantly fewer reconstructive surgeries. Because this was demonstrated for melanomas at difficult anatomic locations, there is no plausible reason to assume it could not be extrapolated to all other sites. Finally, our findings provide support for prospective randomized clinical trials to definitively answer the important question about appropriate margins for melanomas >2 mm in thickness.

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