Margins of Melanoma Excision and Modifications to Standards

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KEYWORDS

• Melanoma • Excision • Margins • Mohs

KEY POINTS

- Excision margins are based on measured clinical margins at the time of surgery and vary depending on the depth of the primary melanoma.
- Certain melanoma subtypes, locations, cosmetic, or functional considerations may require modifications to standard resection margins.
- Mohs microscopic surgery has shown high local control rates, but remains an experimental treatment modality.

INTRODUCTION

Wide local excision of the primary lesion continues to be the mainstay of treatment for primary cutaneous melanoma. However, the extent of the excision has changed significantly over time. Debate surrounding the adequacy of excision margins dates to the late nineteenth century when surgeons, noting the aggressive nature and poor prognosis of the disease, recommended radical excision margins.[1,2] Furthermore, some surgeons advocated for extensive lymph node dissection to be performed in continuity with wide local excision such that, "all that is, removed should be in one continuous strip as far as possible."[3] This approach was supported in a landmark 1907 article published in *The Lancet* by Dr William Handley where he proposed wide margins to include fascial lymphatic vessels.[4] Over the ensuing decades, surgical margins extended out to 5 cm and many times included radical amputation. Evidence supporting such radical excisions came from studies such as the one by Olsen,[5] which reported atypical melanocytes up to 5 cm away from the primary

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melanoma. She advocated for very wide excision margins to decrease the risk of local recurrence.[5]

During the early and mid-twentieth century, significant variation existed in the prognosis of cutaneous melanoma; reliable primary lesion characteristics were lacking. The unpredictable nature of the disease was, in part, a driving factor behind the practice of radical excision. However, studies by Trapl, Clark, and Breslow in the late 1960s found that vertical growth, and more specifically the depth of tumor invasion and tumor thickness, was a better prognostic factor than tumor size as determined by lesion diameter.[6–9] This belief was reflected in the American Joint Committee on Caner first edition using the level of primary lesion invasion and the thickness of penetration as the 2 factors determining primary tumor classification.[10] During this time, opposition to radical excision grew as evidence began to demonstrate similar survival rates with more conservative resection margins in certain patient populations. In his 1970 study establishing tumor thickness as a significant prognostic factor, Breslow[9] argued that patients with lesions less than 0.76 mm may be spared the morbidity of a prophylactic lymph node dissection, a common practice at the time. In a follow-up study in 1977, Breslow and Macht[11] found zero recurrences in 62 patients with thin melanomas (<0.76 mm), regardless of resection margin. In this study, 32% of patients had resection margins of 1.0 cm or less. The prognostic value of the histologic criteria introduced by these authors led to further investigation into the safety of more conservative margins.

Balch and colleagues[12] found no local recurrences in patients with primary melanomas less than 0.76 mm thick regardless of skin margins excised. Margins varied from 0.5 cm to 5.0 cm and 30% were less than 3.0 cm. They proposed a 2-cm excision margin with primary closure in patients with lesions less than 0.76 mm. Furthermore, investigators from the Sydney Melanoma Unit reviewed 1839 patients with stage I melanoma after wide local excision and 5-year follow-up.[13] In patients with thin lesions (0.1–0.7 mm), local recurrence rates were 0.6% in patients with excision margins of 2 cm or greater and 1.9% in patients with more narrow resection margins. The authors concluded that narrow excision margins were just as adequate for local disease control as wide excision margins in patients with thinner lesions. Finally, another large retrospective analysis by Urist and coauthors[14] evaluated the influence of surgical margins and prognostic factors for local recurrence in 3445 patients. In a subgroup analysis of 1151 consecutive patients with melanomas less than 1 mm thick, the authors found only 1 recurrence over the study time period despite excision margins of 2 cm or less in 62% of patients.[14]

Over the ensuing decades, prospective, randomized trails supported the conclusions of these earlier retrospective studies regarding the safety of more conservative excision margins guided by primary tumor characteristics. In this article, we discuss the data establishing current recommendations for surgical margins in primary melanoma and the circumstances when excision margins may be modified.

MELANOMA EXCISION STANDARDS

Cutaneous melanoma incidence has increased worldwide. Histologic factors of the primary lesion, specifically Breslow thickness and the presence or absence of ulceration, as well as nodal status drive melanoma-specific survival and, subsequently, melanoma staging. In the eighth edition of the American Joint Committee on Cancer Melanoma Staging System, the T stage is determined by the Breslow thickness with slight modification based on the presence of ulceration. Similarly, current standards regarding surgical excision margins are guided by the thickness of the primary

lesion. In patients with resectable melanoma, current best practice guidelines support wide local excision of the primary lesion down to but not including the underlying fascia, with horizontal excision margins extending from the edge of the lesion, or biopsy site, up to, but not exceeding, 2 cm depending on the thickness of the primary lesion as permitted by anatomic, functional, or cosmetic considerations. Although certainly not settled, the recommendations are guided by multiple prospective randomized trials with long-term follow-up (**Table 1**).

The first published prospective randomized trial examining excision margins in primary melanoma was conducted by the World Health Organization Melanoma Program and began accrual in 1980.[15] In this multinational trial, 612 patients with primary melanoma no thicker than 2 mm were randomized to receive excision margins of either 1 cm or at least 3 cm. Disease-free and overall survival rates at 55 months were similar between the 2 study groups. Three patients had a local recurrence, all in the narrow margin group and all with a primary melanoma thickness of 1.0 mm or more. No local recurrences occurred in the wide excision group. In 1991, the authors published an updated analysis with a mean follow-up period of 90 months and found similar disease-free and overall survival rates.[16] The authors concluded, based on the absence of local recurrence in patients with a primary melanoma less than 1.0 mm and the very low rate of local recurrence overall, that 1-cm narrow margins are safe in patients with primary lesions no thicker than 2 mm.

Two prospective trials in Europe also examined patients with primary melanoma no thicker than 2 mm, but randomized patients to receive either 2 cm or 5 cm surgical margins.[17,18] First, the French Group of Research on Malignant Melanoma enrolled 337 patients from 9 European centers with a median follow-up time of 192 months. Local disease recurrence occurred in 4 patients who had a wide excision and 1 patient with a narrow excision. All local recurrences occurred in patients with primary lesions greater than 0.94 mm thick. No difference was found in 10-year disease-free or overall survival rates between the 2 study groups. The authors reported that 2-cm surgical margins were sufficient in patients with primary lesions 2 mm or less.[17]

The second European study was performed by the Swedish Melanoma Study Group and included 769 patients with a primary melanoma thickness ranging from

Table 1
Randomized trials evaluating surgical margins after wide local excision of melanoma

Trial	Year	n	Follow-up (Years)	Thickness (mm)	Excision Margins Compared (cm)	Survival
World Health Organization[15,16]	1988/1991	612	4.6/8	≤2.0	1 vs ≥ 3	NS
France[17]	2003	326	16	≤2.0	2 vs 5	NS
Sweden[18,19]	1996/2000	769/989	5.8/11	>0.8–2.0	2 vs 5	NS
Intergroup[20,21]	1993/2001	468	6/10	1.0–4.0	2 vs 4	NS
Sweden[24]	2011/2019	936	6.7/19.6	>2.0	2 vs 4	NS
UK[22,23]	2004/2016	900	5/8	≥2.0	1 vs 3	NS[a]

Abbreviation: NS, not significant.

[a] Analysis after median follow-up at 8.8 years showed a significant difference in melanoma-specific survival (unadjusted hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.01–1.53; $P = .041$) favoring 3-cm margins but no difference in overall survival (unadjusted HR, 1.14; 95% CI, 0.96–1.36; $P = .14$).

0.8 mm to 2 mm. Seven local occurrences occurred, 3 in the narrow excision (2 cm) group and 4 in the wide excision (5 cm) group. No recurrences occurred in patients with a primary lesion thinner than 0.9 mm. Local and regional recurrence rates, as well as 5-year overall survival rates, were similar between study groups.[18] Long-term results from the Swedish Study Group included more patients (989) and a median follow-up period of 11 years. Local recurrence rates remained rare and no difference in survival was found between the study groups.[19]

The first randomized trial to investigate surgical margins in patients with intermediate thickness melanoma (1–4 mm) was conducted by Balch and colleagues.[20] They examined 486 patients, randomized to undergo surgical resection of either 2-cm or 4-cm margins. At a median follow-up time of 6 years, the rates of local recurrence and overall survival were not significantly different between study groups. The authors did find a significantly shorter length of stay in the 2 cm excision group, driven by the decreased need for skin grafting. Long-term results, with a median follow-up time of 10 years, also found no difference in local recurrence or overall survival between study groups.[21] However, the group reported that the presence or absence of ulceration profoundly influenced local recurrence rates. Overall, the authors concluded that 2-cm excision margins were safe in patients with 1- to 4-mm-thick primary melanoma. Together, these studies suggest that, owing to the low recurrence rates in primary melanoma lesions less than 2 mm, more conservative margins of 1 to 2 cm provide similar oncologic outcomes without the additional morbidity. However, prospective randomized trials directly comparing the safety of 1-cm with 2-cm margins are lacking.

As the push to more conservative resection margins continued, additional prospective studies were needed to elucidate the role of conservative margins in patients with more locally advanced disease. The first prospective study to exclusively include patients with a primary melanoma lesion at least 2 mm thick came from a group with participating institutions predominantly in the United Kingdom.[22] Researchers randomized 900 patients to receive a surgical margin of 1 cm or 3 cm. With a median follow-up time of 60 months, a 1-cm surgical margin was associated with an increase in locoregional recurrence (hazard ratio, 1.26; 95% confidence interval, 1.00–1.59; $P = .05$). However, there was no significant difference in melanoma-specific survival or overall survival between the 2 excision groups. Long-term data published by this group demonstrated lower melanoma-specific survival for patients in the 1-cm margin group (unadjusted hazard ratio, 1.24; 95% confidence interval, 1.01–1.53; $P = .041$), but the difference in overall survival was not significant.[23] The authors did note that surgical complications were nearly double in the 3-cm group (8% vs 15%). Overall, the authors suggested that 1 cm margins were inadequate for cutaneous melanoma thicker than 2 mm.

A second study examining patients with a primary melanoma lesion thicker than 2 mm randomized 936 patients over a 12-year period to undergo surgical resection with either a 2-cm or 4-cm margin.[24] After a median follow-up of 6.7 years, the melanoma-specific survival and overall survival were not significantly different between the 2 resection groups. Long-term data with a median follow-up period of 19.6 years confirmed the findings of the earlier study. The authors reported that 2-cm excision margins in patients with primary melanoma thicker than 2 mm was safe.

The final randomized trial worth discussing is the MelMarT trial published in 2018. In this feasibility study, 400 patients with stage T2 to T4 melanomas were randomized between and 1-cm and a 2-cm margin. This trial was not powered to examine local recurrence rates. However, the authors observed that there was a significantly higher rate of reconstruction in the 2 cm margin group (35% vs 14%; $P<.0001$), and the wound necrosis rate in the 2-cm margin cohort was significantly increased

(3.6% vs 0.5%; $P = .036$). Additionally, there was no difference in quality of life between the 2 groups at 12 months follow-up.[25]

A Cochrane review as well as a systematic review and meta-analysis have been performed of these randomized trials.[26,27] Although there are concerns over study heterogeneity, several conclusions can be drawn (**Table 2**). First, excision margins greater than 2 cm should generally be avoided.[26] Additionally, there are more data to support a 2-cm margin than a 1-cm margin for melanomas more than 1 mm thick, but no randomized studies have ever been done to perform a head-to-head comparison.[26,27] Across Europe and in the United States, general surgical excision margins are 1 cm for primary melanoma less than 1 mm thick and 2 cm for lesions thicker than 2 mm. For patients with melanoma between 1 and 2 mm thick, there is considerable variability in practice with surgeons choosing between a 1-cm and a 2-cm excision margin depending on prognostic characteristics and location. Several questions remain regarding appropriate surgical margins. Currently accruing patients is a phase III, multicenter, randomized controlled trail sponsored by Melanoma and Skin Cancer Trials, the national cooperative trials group of Australia and New Zealand, which is investigating 1-cm versus 2-cm surgical margins in patients with stage II (thickness >2 mm or 1- to 2-mm thick lesions with ulceration) primary melanoma (NCT03860883). Hopefully this study, a follow-up to the MelMarT study, will provide clarity for appropriate surgical margins in patients with thicker primary lesions and lesions with aggressive histologic features.

MODIFICATION TO EXCISION STANDARDS

Wide local excision with appropriate margins is the standard treatment for primary melanoma that is surgically resectable; however, owing to anatomic, functional, or subtype considerations, modification to the standard margins may be necessary. Unfortunately, a paucity of prospective data exists to guide appropriate melanoma resection margins in sensitive areas such as the face or distal extremities. Owing to functional or cosmetic considerations, even 1-cm margins may be difficult to obtain in these locations. Furthermore, there is debate surrounding the appropriate surgical margins in certain melanoma subtypes, as well as melanoma in situ.

Melanoma in situ, defined as cutaneous melanoma confined to the epidermis, and the most common subtype, lentigo maligna, present treatment challenges owing to the tendency to have ill-defined clinical margins in addition to the often, and yet unpredictable, subclinical extension of atypical melanocytes, potentially several centimeters beyond the clinical margins.[28] In patients with contraindications to surgical resection or significant cosmetic concerns owing to tumor location, alternatives include topical therapies (eg, imiquimod) or radiation. There is a lack of high-quality evidence

Table 2
Recommended excision margins in primary melanoma

Breslow Thickness	T Stage	Excision Margin (cm)
Melanoma in situ	Tis	0.5–1.0
≤1.0 mm	T1	1.0
>1.0–2.0 mm	T2	1.0–2.0
>2.0–4.0 mm	T3	2.0
>4.0 mm	T4	2.0

comparing nonsurgical and surgical treatment, but high histologic clearance and low recurrence rates have been achieved in experimental settings with experienced providers and close follow-up.[29–31]

Topical imiquimod has emerged as a therapeutic option as a neoadjuvant, adjuvant, or monotherapy treatment modality, especially in patients with lentigo maligna. In a retrospective review, Donigan and colleagues[32] reported a 3.9% recurrence rate at a mean time of 4.3 years in 334 patients with lentigo maligna who received imiquimod followed by planned surgical excision (median final margin of 2 mm). Swetter and coauthors[33] administered imiquimod as primary therapy (n = 22) or adjuvant therapy (n = 36) in patients with narrowly excised or histologically positive margins in the setting of lentigo maligna. At a mean follow-up period of 42 months, 16 patients (72.7%) in the primary therapy group and 34 patients (94.4%) in the adjuvant group demonstrated clinical clearance.[33] A literature review including 349 patients with lentigo maligna who received primary radiation therapy reported 18 recurrences (5%) over a median follow-up of 3 years.[31] Five patients had disease progression to lentigo maligna melanoma. Further studies are needed to clarify the role of nonsurgical treatments for melanoma in situ; however, current data suggest that reliance on topical or radiation therapies alone may put the patient at increased risk for local recurrence.

Historical guidelines recommended wide excision with 5-mm margins in patients with melanoma in situ; however, evidence suggests margins up to 1 cm are needed for adequate disease clearance, especially in lentigo maligna. A prospective cohort study of 2335 patients with melanoma in situ demonstrated clearance rates of 79% for lentigo maligna and 83% for nonlentigo maligna melanoma in situ with 6-mm margins. To achieve a 97% clearance rate for all melanoma in situ subtypes, a 12-mm margin was required on the head and neck and a 9-mm margin on the trunk and extremities.[34] As a result, current National Comprehensive Cancer Network guidelines recommend 0.5- to 1.0-cm margins for all melanoma in situ.

A growing body of evidence supports the use of Mohs microscopic surgery (MMS) for melanoma in situ in certain patient populations such as those with lentigo maligna of the face. Nosrati and colleagues[35] examined 662 patients retrospectively with melanoma in situ comparing wide local excision to MMS. They found no difference in 5-year recurrence rates, overall survival, or melanoma-specific survival. Furthermore, the use of MMS has increased in recent years and was the treatment modality of choice in more than 3% of all Surveillance, Epidemiology, and End Results–documented melanoma excisions from 2003 to 2008.[36] Chin-Lenn and colleagues[37] conducted a retrospective review comparing MMS (60 patients) and wide local excision (91 patients) in 151 patients with invasive melanoma of the face. The 5-year recurrence and disease-specific survival rates were not significantly different between resection techniques. On multivariable analysis, Breslow thickness was the only consistent predictor of recurrence or disease-specific survival. Overall, data on MMS are limited to retrospective review; prospective randomized trials are needed to clarify the ability of MMS to achieve high clearance and low recurrence rates before this approach can be considered a standard treatment option.

Primary melanoma located on the distal extremities in subungual sites, as well as the palms and soles, also present challenges to appropriate wide excision. In a retrospective review of 46 patients with subungual melanoma, the level of amputation did not affect survival or the incidence of local recurrence.[38] As a result, conservative amputation of the affected digit at the most distal interphalangeal or metatarsophalangeal joint is appropriate. In patients with plantar or palmar melanoma, the deep fascia should be preserved. These wounds are rarely closed primarily and generally require skin grafting or more extensive soft tissue coverage.

Certain melanoma subtypes, owing to their aggressive nature, may require larger resection margins than similarly sized cutaneous lesions. For example, desmoplastic lesions more commonly occur on the head and neck, are more locally aggressive, and may surround or directly invade nerves.[39] A retrospective review of 242 patients with either pure or mixed desmoplastic melanoma found that pure desmoplastic melanoma excised with 1-cm margins had higher incidences of local recurrence and mortality.[40] The authors recommended 2-cm margins even for thin lesions. Occasionally, radiation therapy is used as an adjunct to wide local excision of desmoplastic melanoma. A recent review of the National Cancer Database demonstrated a significantly improved overall survival for patients with desmoplastic melanoma treated with wide local excision plus radiation therapy compared with excision alone in multivariate analysis and propensity matching.[41]

Primary mucosal melanoma is a rare subtype, generally presenting at a more advanced stage, and has a worse 5-year survival than cutaneous or ocular melanoma.[42] Owing to the poor prognosis of these melanomas, treatment is conservative, favoring local excision instead of radical resection (ie, local resection instead of abdominoperineal resection for rectal mucosal melanoma). Radiation therapy does not improve survival but may improve locoregional control.

SUMMARY

Multiple prospective, randomized trials have demonstrated that less radical excision margins of primary cutaneous melanoma are noninferior and provide similar local recurrence and overall survival compared with more radical excision margins when guided by tumor depth. However, additional clinical trials are needed to clarify excision margins in certain patient populations, including those with lesions of intermediate thickness, aggressive characteristics, or located in cosmetically or functionally sensitive areas. Finally, although alternatives to wide local excision of the primary lesion exist, these techniques are still experimental and additional studies are needed to fully evaluate the efficacy of these treatment modalities.

DISCLOSURE

A. Berger has served on the Speaker's Bureau for Cardinal Health (Lymphoseek) and on Advisory Board for Castle Biosciences, Inc.

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