Updated evidence-based clinical practice guidelines for the diagnosis and management of melanoma: definitive excision margins for primary cutaneous melanoma

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Abstract

Introduction: Definitive management of primary cutaneous melanoma consists of surgical excision of the melanoma with the aim of curing the patient. The melanoma is widely excised together with a safety margin of surrounding skin and subcutaneous tissue, after the diagnosis and Breslow thickness have been established by histological assessment of the initial excision biopsy specimen. Sentinel lymph node biopsy should be discussed for melanomas ≥ 1 mm thickness (≥ 0.8 mm if other high risk features) in which case lymphoscintigraphy must be performed before wider excision of the primary melanoma site. The 2008 evidence-based clinical practice guidelines for the management of melanoma (http://www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/ClinicalPracticeGuidelines-ManagementofMelanoma.pdf) are currently being revised and updated in a staged process by a multidisciplinary working party established by Cancer Council Australia. The guidelines for definitive excision margins for primary melanomas have been revised as part of this process.

Main recommendations: The recommendations for definitive wide local excision of primary cutaneous melanoma are:

- melanoma in situ: 5–10 mm margins
- invasive melanoma (pT1) ≤ 1.0 mm thick: 1 cm margins
- invasive melanoma (pT2) 1.01–2.00 mm thick: 1–2 cm margins
- invasive melanoma (pT3) 2.01–4.00 mm thick: 1–2 cm margins
- invasive melanoma (pT4) > 4.0 mm thick: 2 cm margins

Changes in management as a result of the guideline: Based on currently available evidence, excision margins for invasive melanoma have been left unchanged compared with the 2008 guidelines. However, melanoma in situ should be excised with 5–10 mm margins, with the aim of achieving complete histological clearance. Minimum clearances from all margins should be assessed and stated. Consideration should be given to further excision if necessary; positive or close histological margins are unacceptable.

Definitive management of primary cutaneous melanoma consists of surgical excision of the melanoma with the aim of curing the patient. After initial excision biopsy to establish the diagnosis and determine Breslow thickness, surgical management involves wide local excision of the surrounding skin and subcutaneous tissue with a safety margin of normal looking skin. The aim is to completely remove all invasive and in situ melanoma, as well as any micro-metastases that might be present in the marginal skin. If all the malignant cells are removed and there is no spread to lymph nodes or other sites, the procedure should be curative.

Complete excision should be confirmed by histological examination of the excised specimen, with special reference to the periphery. When present, the in situ component (which can be invisible to the naked eye) often extends beyond the invasive melanoma, and complete excision of both with the recommended margins is mandatory.

The width of surgical excision is important because of the potential trade-off between improved cosmesis and inferior long term (morbidity and mortality) outcomes if margins are inadequate.

Recommendations for radial excision margins used in wide local excision are based on the Breslow thickness of the primary melanoma at its thickest depth of invasion. Generally, thicker melanomas and those with less favourable prognostic features are excised with wider margins. Sentinel lymph node biopsy (SLNB) should be discussed for melanomas ≥ 1 mm thickness (≥ 0.8 mm if there are other high risk features), in which case lymphoscintigraphy must be performed before wider excision of the primary melanoma site (as recommended in the national guidelines on SLNB[1]).

Methods

The 2008 evidence-based clinical practice guidelines for the management of melanoma (http://www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/ClinicalPracticeGuidelines-ManagementofMelanoma.pdf) are currently being revised and updated in a staged process by a multidisciplinary working party established by Cancer Council Australia. As part of this process, the guidelines for definitive excision margins for primary melanomas have been revised.[2] A chapter group of the working party established by Cancer Council Australia undertook a detailed literature review and critically appraised all available evidence relating to melanoma excision margins. Draft evidence-based recommendations and practice points were developed, then circulated for public comment and consultation.

The final document was ratified by the entire membership of the Cancer Council Australia Melanoma Guidelines Working Party and published on the Cancer Council Australia website in a Wiki format that can readily be updated as new evidence becomes available.[3]

The evidence summary, recommendations and practice points are listed in Box 1, Box 2 and Box 3. Details of the methodological processes, levels of evidence and grades of recommendation used for guideline development are available at http://wiki.cancer.org.au/australia/Guidelines:Melanoma/Guideline_development_process.

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1 Melanoma excision margins: evidence summary

Evidence	Level*
There is case series evidence suggesting that 5 mm margins are inadequate for many cases of melanoma in situ and may lead to significant rates of disease recurrence.[25-30]	IV
There is no convincing RCT evidence that a margin greater than 2 cm offers additional benefit for the patient in terms of overall survival or local recurrence, irrespective of melanoma thickness.[4-15]	I, II
Two RCTs show evidence that a margin greater than 1 cm offers no survival advantage, although it is not clear whether a wider margin reduces the risk of local recurrence.[6,9]	II
Systematic reviews indicate that there are currently inadequate data to confirm a mortality difference between wider and narrower excision for primary invasive melanoma.[10-15]	I
For acral lentiginous and subungual melanomas there are no RCTs or systematic reviews to define excision margins. Data are from retrospective case studies. There are limited RCT data for head and neck melanoma with the majority of data also derived from retrospective case series. Excision margins might be modified to accommodate individual anatomic sites or functional considerations, but this practice would be based on case series information and individual factors rather than on RCT evidence, which is currently lacking.[37-43]	III-2, IV

RCT = randomised controlled trial. * For details of the methodological processes, levels of evidence and grades of recommendation used for guideline development, see http://wiki.cancer.org.au/australia/Guidelines:Melanoma/Guideline_development_process. ◆

Results and recommendations

Currently, the exact extent of surgical excision margins that should be used for a given thickness of melanoma and the magnitude of benefit for different margins remain unclear, because the various trials have used different criteria, and 1 cm *v* 2 cm excision margins have not yet been directly compared for invasive melanomas. As a result, the question of what precise margin is minimal or optimal to be safe awaits a definitive answer. However, six randomised controlled trials (RCTs) including a total of 4233 participants provide useful data based upon outcomes for surgical excision margins according to the Breslow thickness of invasive melanomas.[4-9] All six RCTs assessed width of excision but did not consider depth of excision. These trials compared narrow (1–2 cm) versus wide (3–5 cm) excision margins and assessed outcomes including overall survival, melanoma-specific survival and local recurrence rates, with median follow-up ranging from 5 to 16 years. However, definitions of local recurrence have often been inconsistent or unstated, and the impact on patient survival has been unclear, so local recurrence data must be interpreted with caution. The RCTs have been further assessed in six systematic reviews and meta-analyses.[10-15] There have also been several large published case series that provide further data.[16-22]

No RCTs have assessed depth of excision. Recent non-randomised studies suggest that excision of the deep fascia does not improve the outcome for melanomas thicker than 1 mm[23] or 2 mm;[21] however, results of these retrospective studies must be interpreted with caution. The depth of excision in usual clinical practice is excision down to but not including the deep fascia, unless the fascia is involved with tumour or if removal of it is technically warranted.

Melanoma in situ

There are no RCTs and limited case series data to help guide optimal excision margins for melanoma in situ.[24] Based on the sparse evidence available, the 2008 clinical practice guidelines[2] recommended 5 mm excision margins for melanoma in situ. However, a number of recent studies have shown that 5 mm margins may be inadequate and lead to significant rates of recurrence, with several authors suggesting that at least 10 mm margins are required for in situ melanomas.[25-30]

One of the largest of these studies[25] assessed complete clearance of 1120 in situ melanomas excised by Mohs surgery. Complete tumour clearance rates were 86% for 6 mm margins, 98.9% for

2 Melanoma excision margins: evidence-based recommendations*

Melanoma in situ (grade D)
After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 5–10 mm (measured with good lighting and magnification) with the aim of achieving complete histological clearance. Melanoma in situ of non-lentigo maligna type is likely to be completely excised with 5 mm margins, whereas lentigo maligna may require wider excision.

Invasive melanoma (pT1) < 1.0 mm (grade B)
After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1 cm.

Invasive melanoma (pT2) 1.01–2.00 mm (grade B)
After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1–2 cm.

Invasive melanoma (pT3) 2.01–4.00 mm (grade B)
After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1–2 cm.
Caution should be exercised for melanomas 2.01–4.00 mm thick, especially with adverse prognostic factors, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2 cm) for these tumours depending on the tumour site and characteristics, and prevailing surgeon/patient preferences.

Invasive melanoma (pT4) > 4.0 mm (grade B)
After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 2 cm.

Melanomas at sites other than the trunk and proximal limbs
Acral lentiginous and subungual melanoma are usually treated with a minimum margin as set out above, where practicable, including partial digital amputation usually incorporating the joint immediately proximal to the melanoma (grade D).
Excision margins might be modified to accommodate individual anatomic sites or functional considerations, but this practice would be based on case series information and individual factors rather than on RCT evidence, which is currently lacking (grade D).

For all melanomas
Minimum clearances from all margins should be stated and assessed. Consideration should be given to further excision if necessary; positive or close histological margins are unacceptable.

* For details of the methodological processes, levels of evidence and grades of recommendation used for guideline development, see http://wiki.cancer.org.au/australia/Guidelines:Melanoma/Guideline_development_process. ◆

3 Practice points

- Excisions should have vertical edges to ensure consistent margins.
- For all melanomas, the clinical (surgical) radial excision margins are measured from the edge of the melanoma (or scar). The total radial margin should be the sum of the initial primary melanoma margin and the wider excision margin.*
- Excision biopsy of the complete lesion with a narrow margin (2–5 mm) is appropriate for definitive diagnosis of primary melanoma. Once the diagnosis of melanoma has been made, re-excision of the lesion (scar) should then be performed in order to achieve the definitive wider margins recommended in these guidelines.
- For all melanomas, minimum clearances from all margins should be stated and assessed on the pathology report.
- For all melanomas, a final assessment of excision margins should be made in light of the histological margins. Consideration should be given to further excision if necessary because positive or close histological margins are unacceptable.
- If sentinel lymph node biopsy is contemplated in the management of thicker melanomas, the definitive wide excision should not be undertaken before lymphatic mapping and biopsy have been performed.
- Depth of excision in usual clinical practice is excision down to but not including the deep fascia unless it is involved or has been reached during the diagnostic excision. For body sites where there is particularly deep subcutis, it is usual practice to excise to a depth equal to the recommended lateral (radial) excision margins for that specific melanoma; in these cases it is not deemed necessary to excise right down to fascia.
- Where tissue flexibility is limited, a flap repair or skin graft is often necessary subsequent to an adequate margin of removal.
- Most melanomas can be treated as outpatient or day cases under local anaesthesia.
- Patients should be informed that surgical excision may be followed by wound infection, bleeding, haematoma, failure of the skin graft or flap, risk of numbness, a non-cosmetic scar, dehiscence and the possibility of further surgery.
- Some tumours may be incompletely excised despite using the above-recommended margins. These include melanomas occurring in severely sun-damaged skin (eg, lentigo maligna) and those with difficult-to-define margins (eg, amelanotic and desmoplastic melanomas). In these categories, the presence of atypical melanocytes at the margins of excision should be detected by comprehensive histological examination (including immunohistochemical staining) and followed by wider excision.
- Amelanotic melanoma can present significant difficulties for defining a margin, with up to one-third of subungual and nodular melanomas being non-pigmented. This may dictate choice of a wider margin or further re-excision where practicable.
- For patients with deeper invasive melanomas (> 1 mm thick), referral to a specialised melanoma centre should be considered to ensure that best practice is implemented and for the collection of national outcome data. This may present logistic difficulties in regional and remote areas, but specialist care is recommended.

* This method of measurement has been practised and reported in all six published randomised controlled trials.[4-9] ◆

9 mm margins, 99.4% for 12 mm margins, 99.6% for 15 mm margins and 100% for 30 mm margins. The authors concluded: "The frequently recommended 5 mm margin for melanoma in situ is inadequate. Standard surgical excision of melanoma in situ should include 9 mm of normal-appearing skin, similar to that recommended for early invasive melanoma".[25]

As the microscopic extent of lentigo maligna and melanoma in situ can be difficult to determine clinically, dermoscopy and confocal microscopy may be useful in defining margins before excision of melanoma in situ.[31,32]

Like the 2008 Australian guidelines, the 2010 UK guidelines recommended 5 mm margins[33] but the 2011 US guidelines recommended 5–10 mm margins and stated that wider margins may be necessary for lentigo maligna subtypes.[34] The recent studies cited above support this recommendation.

Recommendation: For melanoma in situ, excision margins should be 5–10 mm, with the aim of achieving complete histological clearance.

Melanomas ≤ 1 mm thick

There have been no RCTs which only evaluated melanomas ≤ 1 mm thick. However, three of the RCTs that assessed melanomas ≤ 2 mm thick included patients with melanomas ≤ 1 mm thick. These were a French trial (159 participants had melanomas ≤ 1 mm thick),[4] a 1982 Swedish trial (244 participants had melanoma ≤ 1 mm thick)[5] and the World Health Organization (WHO) trial (359 participants had melanomas ≤ 1 mm thick).[6] No reduction in mortality was found for wider excision (5 cm in the French study,[4] 5 cm in the Swedish study,[5] 3 cm in the WHO study[6]) compared with narrower excision (2 cm in the French study,[4] 2 cm in the Swedish study,[5] 1 cm in the WHO study[6]). Of note, just 185 participants in the WHO trial were treated with 1 cm margins.[6]

A recently published case–control study of 11 290 patients with thin melanomas (≤ 1 mm thick) showed that local recurrence was associated with < 8 mm histological excision margins (corresponding to < 1 cm margins in vivo), suggesting that a ≥ 1 cm clinical excision margin for thin melanomas reduces the risk of local recurrence.[16]

Although there is limited information on which to base clinical recommendations for excision margins for melanoma ≤ 1 mm thick, most international guidelines recommend 1 cm excision margins for melanoma ≤ 1 mm thick, and this is generally deemed standard management.

Recommendation: For melanomas ≤ 1.0 mm, excision margins should be 1 cm.

Melanomas 1.01–2.00 mm thick

Four RCTs, including 1429 patients in total, assessed melanomas between 1 mm and 2 mm thick: Khayat and colleagues (the French study; 167 participants);[4] Cohn-Cedermark and colleagues (the 2000 Swedish study; 745 participants);[5] Cascinelli (the WHO study; 245 participants);[6] and Balch and colleagues (the Intergroup study; 272 participants).[7] None of these trials showed a statistically significant difference in overall survival between the two groups of patients who were managed with either wide excision (5 cm in the French study,[4] 5 cm in the Swedish study,[5] 3 cm in the WHO study,[6] 4 cm in the Intergroup study[7]) or narrow excision (2 cm in the French study,[4] 2 cm in the Swedish study,[5] 1 cm in the WHO study,[6] 2 cm in the Intergroup study[7]). Of note, only 113 participants (in the WHO study[6]) were treated with 1 cm excisions.

Three retrospective studies[17-19] have assessed the width of excision margins for melanomas ≤ 2 mm thick, but the magnitude of any potential associations is difficult to understand, due to the need for multivariate adjustment for confounding by other risk factors. A large single-centre retrospective study of 2681 patients with cutaneous melanomas ≤ 2 mm thick suggested that a 1 cm clinical margin was adequate in terms of both local recurrence and survival.[17] In another large single-centre retrospective study of 2131 patients with primary cutaneous melanomas 1.01–2.00 mm thick, pathologic excision margins of < 8 mm were associated with worse regional node recurrence-free survival and distant recurrence-free survival compared with margins ≥ 8 mm corresponding to ≥ 1 cm surgical margins), but did not translate into a statistically significant difference in melanoma-specific survival.[18] In another retrospective single-centre series of 576 patients with 1–2 mm thick melanomas, 1 cm margins were associated with a small increase in local recurrence compared with 2 cm margins but no change in overall survival.[19]

There are limited data on excision margins for melanomas 1.01–2.00 mm thick to help differentiate between 1 cm and 2 cm margins. Most international guidelines recommend either 1 cm excision margins or 1–2 cm excision margins for 1.01–2.00 mm thick melanomas.

It is important to note that if SLNB is contemplated, the definitive wide excision should not be undertaken before lymphatic mapping and biopsy have been performed.

Recommendation: For melanomas 1.01–2.00 mm thick, excision margins should be 1–2 cm.

Melanomas 2.01–4.00 mm thick

Three RCTs included patients who had melanomas 2–4 mm thick and included a total of 1516 patients. These were the Intergroup study (190 participants),[7] the 2011 Swedish study (666 participants)[8] and the United Kingdom Melanoma Study Group (UKMSG) study (about 660 participants).[9] None of these trials showed a statistically significant difference in overall survival between the two groups who were managed with either wide excision (4 cm in the Intergroup study,[7] 4 cm in the Swedish study,[8] 3 cm in the UKMSG study[9]) or narrow excision (2 cm in the Intergroup study,[7] 2 cm in the Swedish study,[8] 1 cm in UKMSG study[9]).

The UKMSG study showed a statistically significant increased loco-regional recurrence rate in the 1 cm margin versus 3 cm margin groups, but this appeared to be due to regional nodal metastasis rather than local and in-transit recurrence.[35] A recent update of this trial showed a statistically significant improvement in melanoma-specific survival in favour of 3 cm wide excision compared with narrow excision (hazard ratio, 1.24; 95% CI, 1.01–1.53; $P = 0.041$) but no statistically significant difference in overall survival between the two groups (hazard ratio, 1.14; 95% CI, 0.96–1.36; $P = 0.14$).[9] Interpretation of this modest melanoma-specific survival improvement in the absence of any significant difference in overall survival is difficult. Of note, melanoma-specific survival and overall survival were both secondary outcomes in this study. Accurate measurement of melanoma-specific survival is more difficult than measurement of overall survival because it relies on accurate information about cause of death. Given that a significant number of melanomas in the UKMSG study were thick melanomas (> 4 mm), it is unclear whether this influenced the overall study results. In an accompanying editorial, it was suggested that "the excess nodal disease in the narrow margin group was indicative of poor prognostic disease before the intervention, rather than resulting from the narrow margin intervention itself".[36] Unfortunately, this assumption cannot be tested because only 27 of the 900 patients in the UKMSG study had pathological node staging by SLNB.[9]

In a single-centre retrospective review of 1587 patients with melanomas 2.01–4.00 mm thick, histological margins ≥ 8 mm (equivalent to a ≥ 1 cm surgical margin) were associated with increased local and in-transit recurrence-free survival and disease-free survival compared with a < 8 mm margin.[20] Another retrospective single-centre cohort study of 325 patients with melanomas > 2 mm thick evaluating 1 cm or 2 cm excision margins showed no significant differences in loco-regional and distant metastasis, disease-free survival and overall survival between the groups.[21]

No difference in overall survival when comparing 4 cm and 2 cm margins in the Intergroup study[7] and the 2011 Swedish study[8] suggests that margins greater than 2 cm are not beneficial for thick melanomas. Indeed, there is no convincing RCT evidence that a margin greater than 2 cm offers additional benefit for the patient in terms of overall survival or local recurrence, irrespective of melanoma thickness. The clinical significance of the modest improvement in melanoma-specific survival in the UKMSG study[9] in the 3 cm excision group compared with the 1 cm excision group in the absence of benefit in overall survival remains unclear. On balance, given currently available evidence, the updated guidelines continue to recommend 1–2 cm excision margins for melanomas of Breslow thickness 2–4 mm (unchanged from the 2008 guidelines). However, caution should be exercised favouring 2 cm excision margins in this group, especially if other adverse features such as ulceration or a high mitotic rate are present.

Again, if SLNB is contemplated, the definitive wide excision should not be undertaken before lymphatic mapping and biopsy have been performed.

Recommendation: For melanomas 2.01–4.00 mm thick, excision margins should be 1–2 cm.

Melanomas > 4 mm thick

About 240 patients in the UKMSG study[9] and 270 patients in the Swedish study[8] had melanomas ≥ 4 mm. There was no statistically significant difference in overall survival between the groups managed with wide or narrow excision margins.[8,9] Both studies analysed melanomas > 4 mm as part of the entire cohort, not separately, so it is unclear whether the overall results can be extrapolated to these thicker melanomas.[8,9]

In a retrospective study of 632 clinically lymph node-negative patients with melanomas > 4 mm thick, histopathologically determined primary tumour excision margins > 16 mm (corresponding to 2 cm surgical margins) were associated with better local control compared with narrower margins.[22]

RCT data show that margins > 2 cm (ie, 3, 4 or 5 cm) do not result in superior disease-specific outcomes, despite increased surgical morbidity risk. Other international guidelines suggest excision margins of 2 cm for melanomas ≥ 4 mm thick. Wider margins might be clinically appropriate if other adverse prognostic features are present, although RCT data are lacking.

Once more, if SLNB is contemplated, the definitive wide excision should not be undertaken before lymphatic mapping and biopsy have been performed.

Recommendation: For melanomas > 4.0 mm thick, clinical excision margins should be 2 cm.

Melanomas at sites other than the trunk and proximal limbs

The six published RCTs[4-9] do not satisfactorily assess the subject of melanomas in specific body sites other than the trunk and proximal limbs. Hence, there are limited data on which to guide excision margins for sites such as head, neck and face, genitals, distal extremities, hands and feet (including acral lentiginous, subungual and digital melanomas).

Where practicable, acral lentiginous and subungual melanoma are usually treated with an excision margin as set out above, including partial digital amputation usually incorporating the joint immediately proximal to the melanoma.

Anatomical restrictions and morbidity associated with wider excisions (even 1 cm) at these sites can be problematic. Narrower margins have been advocated, but there are no RCT data to properly confirm safety.

A few non-randomised trials suggest that excision margins on the face (including eyelid and ear), head and neck or digits can be safely reduced but the results must be interpreted with caution given the nature of the studies.[37-43]

Balancing adequate melanoma excision margins for the site and characteristics of the melanoma, while maintaining the optimal preservation of function, would seem sensible.

Conclusion

The updated Australian national guidelines for definitive margins of excision of primary cutaneous melanomas have been developed using an evidence-based process based on the best available current evidence, evaluated by the Cancer Council Australia's Working Party. The guidelines are designed to promote optimal practical management of patients with melanoma in Australia.

Based on currently available evidence, excision margins for invasive melanoma have been left unchanged compared with the 2008 guidelines. However, melanoma in situ should be excised with 5–10 mm margins, with the aim of achieving complete histological clearance. Minimum clearances from all margins should be assessed and stated. Consideration should be given to further excision if necessary; positive or close histological margins are unacceptable. The full recommendations are detailed in Box 2.

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