Clinical and Histological Margins in Melanoma Surgery — Evidence Supplement

This supplement is designed to be read alongside the brief reference document "Clinical and Histological Margins in Melanoma Surgery" which is available at https://www.skincancersymposiums.com/resources along with other resources on this and other topics

What this supplement adds

- The evidence underpinning the 10-30% shrinkage estimate
- Expanded desmoplastic melanoma metastasis data (pure vs. mixed subtype)
- A full breakdown of the six randomised trials and a 2025 population-based cohort study on margin width and survival
- Quality of life and cost evidence relevant to the case for narrower margins
- Guideline definitions (or the lack of one) for a "clear histological margin"
- Whether the >3mm histological margin threshold, established for melanoma in situ, also applies to invasive melanoma
- The anatomical basis for the deep margin, and the evidence behind hair-follicle involvement in MIS
- The fuller evidence base for nonsurgical treatment of lentigo maligna (imiquimod, radiotherapy)
- Eight additional references not in the brief document (9-11 and 16-20 below)

Shrinkage

The 10-30% shrinkage range is supported by several independent studies. Kerns et al. (2008) prospectively measured 97 cutaneous specimens and found shrinkage occurred at two stages: immediately after excision and again after 24-48 hours of formalin fixation (2). de Waal (2021), in

a prospective study with accompanying literature review, found that skin tumour specimens shrink by approximately 20% with excision alone, with a further 11% shrinkage during formalin processing, giving a total shrinkage of roughly 28.6% from the original surgical marking to the final histological measurement (9). The Melanoma Institute of Australia has separately used a 20% shrinkage assumption when correlating histological and clinical margins. Older estimates of up to 40% shrinkage appear to sit at the extreme end of the range reported in more recent, methodologically stronger studies, and are occasionally still reported, but they fall outside what the current evidence supports. For that reason the brief document's floor calculation uses 30% — the upper end of the evidence-based range — as its conservative assumption, rather than the unsupported 40% figure.

Desmoplastic melanoma

The brief document notes that pure desmoplastic melanoma (DM) carries a lower metastatic risk than mixed DM. The supporting numbers: pure DM (≥90% desmoplastic component) has a reported distant metastasis rate of roughly 4-7%, comparable to or lower than conventional melanoma, whereas mixed DM has a reported distant metastasis rate of roughly 14-18.6%, similar to or higher than conventional melanoma (8).

Clinical Deep Margin

Both the Australian/NZ and NCCN guidelines describe the deep margin anatomically — down to and including the subcutaneous fat, stopping at fascia — rather than as a distance that scales with the width of the radial margin. Fascia itself is only excised where it is clinically or histologically involved; there is no evidence that routinely excising uninvolved fascia improves outcomes, even for melanomas thicker than 2mm. Where subcutaneous fat is unusually deep (e.g. an obese abdomen), excision should still reach at least a depth equal to the radial margin, even if this falls short of fascia. Separately, Burger et al. (2023) found that when fascia was not reached, a deep margin of at least ~8mm histologically (~1cm surgically, allowing for shrinkage) was associated with significantly better regional and distant recurrence-free survival than shallower margins (15).

The biological rationale for excising to an equivalent depth in invasive disease and MIS — even though MIS, by definition, remains confined to the epidermis — is well supported: Pozdnyakova et al. (2009) found tumour cells within one or more hair follicles in 82% of melanoma in situ specimens, with atypical melanocytes extending a mean of 0.45mm into the follicle (range 0.1–1.1mm), occasionally as deep as the follicular isthmus (12); a separate study in lentigo maligna reported follicular involvement in 95.8% of specimens. In-situ disease can therefore extend below the epidermis via the follicular epithelium without crossing the basement membrane. Hair follicles themselves often extend deep into the subcutaneous fat — terminal hair bulbs are commonly seated there — so complete removal requires excising down to (but not including) the deep fascia.

Nonsurgical Treatment Options for Lentigo Maligna

The brief document notes that nonsurgical options (imiquimod, radiotherapy, active surveillance) are sometimes used in frail patients or where excision would be functionally or cosmetically unacceptable, and that these lack robust evidence. No randomised controlled trials exist for either imiquimod or radiotherapy in this setting, so that statement is directionally correct, but the retrospective and systematic review evidence is more substantial than a blanket "lacks evidence" conveys, and is worth knowing in full.

Imiquimod: the largest quantitative systematic review (Mora et al., 2015), pooling 347 tumours across 45 studies, found histologic clearance of 76.2% (95% CI 71.4-81.0%) and clinical clearance of 78.3% (95% CI 73.6-82.9%). Recurrence rates ranged from around 2% at approximately three years of follow-up to as high as 21% in studies with longer follow-up, and one cohort of 103 patients followed for 17 years reported sustained clearance in the majority, with recurrences continuing to accrue over time (13). Clearance is dose- and intensity-dependent, meaning outcomes vary meaningfully by treatment protocol.

Radiotherapy: a systematic review (Panje et al., 2020) covering 14 studies and 1,243 lesions (1,075 LM, 168 LMM) found local recurrence rates ranging widely from 0% to 31%, with no prospective trials identified (all evidence retrospective) (14). In several series, radiotherapy recurrence rates were comparable to surgical series; however, at least one single-centre retrospective study found a substantially higher recurrence rate with radiotherapy than with surgical excision (29% vs 4.2%). This variability, more than a simple "lack of evidence," is the more clinically important message: radiotherapy appears to be a reasonable option for patients unsuited to surgery, but is not interchangeable with surgical excision on current evidence.

Margin Width and Survival

The brief document states, deliberately concisely, that the effect of margin width on survival is contested. This section sets out why, in more depth: six completed randomised controlled trials, plus several large meta-analyses and a Cochrane review, have examined whether wider excision margins improve outcomes over narrower ones.

Melanomas up to 2 mm thick: solid evidence

Three randomised trials directly addressed melanomas up to 2mm thick: the WHO/Veronesi trial (1cm v 3cm) (16), the European/Khayat trial (2cm v 5cm, melanomas <2.1mm) (17), and the Swedish I/Cohn-Cedermark trial (2cm v 5cm, melanomas 0.8–2.0mm) (18). All three found no statistically significant difference in overall or disease-free survival between narrower and wider margins, with very low absolute rates of local recurrence in both arms. This body of evidence is the most consistent part of the literature and underpins current guideline margins for thin melanoma.

Melanomas over 2 mm thick: the evidence is mixed

The Intergroup/Balch trial (2cm v 4cm; Balch et al., 2001) enrolled patients with intermediate-thickness melanomas (1–4mm) and found no statistically significant difference in overall or disease-free survival between margins (19). The Scandinavian trial (2cm v 4cm, median follow-up 19.6 years; Utjés et al., 2019) found no significant difference in overall or melanoma-specific survival, supporting a 2cm margin as safe for thicker melanoma (6). However, the UK Melanoma Study Group trial (1cm v 3cm) found, on extended follow-up to a median of 8.8 years, that the 1cm margin was associated with significantly worse disease-specific survival than the 3cm margin (absolute difference 5.95% at 10 years; HR 1.24, 95% CI 1.01-1.53, p=0.041) (7). This finding carries real limitations: no patients were staged with sentinel lymph node biopsy, and statistical significance depended on combining local and regional nodal recurrence, so the difference may partly reflect an imbalance in occult disease burden between arms rather than a true causal effect of margin width. In summary, for margins of 2cm and above, the balance of high-quality randomised evidence shows no survival benefit from further widening, and this is well supported. For narrower margins (particularly 1cm) in thicker melanoma, the evidence is genuinely split, with at least two credible sources (the UK trial and the Buja cohort) suggesting a possible survival cost to very narrow margins. Across nearly all studies, the more consistent finding is that narrower margins are associated with a higher rate of local recurrence, even where this does not translate into a measurable survival difference. The ongoing MelMarT-II trial (1cm v 2cm) was specifically designed to resolve the narrower-margin question with contemporary staging (routine sentinel node biopsy) and adequate statistical power; recruitment closed in August 2025 with over 3,000 patients enrolled.

Quality of Life and Cost Considerations

The case for narrower margins does not rest on survival evidence alone. Wider margins carry a measurable burden: in the MelMarT-I feasibility study, 34.9% of patients in the 2cm arm required reconstruction with a skin graft or flap compared with 13.6% in the 1cm arm (20), and this gap was more pronounced for head and neck lesions. Meta-analyses estimate a number-needed-to-harm of three for reconstruction (i.e., for every three patients given a wider margin, one undergoes a reconstruction that a narrower margin would have avoided). Older trials (Intergroup, Scandinavian) similarly found substantially higher rates of skin grafting, longer hospital stays, and greater surgical morbidity in wider-margin arms, without a matching survival gain in the ≥2cm range. A single-centre UK cost analysis found reconstruction significantly increased both hospitalisation rates and per-patient procedure costs. These considerations are a legitimate and evidence-based part of the case for conservative margins, independent of the survival debate, and are discussed in detail in Orme & Moncrieff's 2024 review (11).

What is a ‘clear histological margin?

The brief document notes that "clear histological margins" lack a universal definition. This remains true across NCCN, AAD, and European guideline documents, which specify clinical (surgical) margins by Breslow thickness but do not define a target histological margin — the reverse-engineering approach in the brief document is a reasonable, but not officially endorsed, way of filling that gap.

Does the >3mm Histological Margin Threshold Apply Beyond Melanoma In Situ?

The >3mm threshold discussed in the brief document is drawn from Moura et al. (2020), which studied melanoma in situ specifically (of note the cohort was 89% lentigo maligna (80% pure and 9% mixed). Direct histological margin/recurrence data for invasive melanoma more broadly remains sparse, which is a genuine gap in the evidence base. The best available extension comes from Hoang et al. (2023), a cohort of 268 invasive lentigo maligna melanomas (LMM) followed for a median of 10.2 years (range 0-31.8 years), which found that positive or close (<3mm) histologic margins independently predicted worse progression-free survival(5). This is weaker evidence than Moura’s: Hoang et al. did not report recurrence rates broken down by margin status, and did not test whether wider thresholds (5mm, 8mm, etc.) predict outcomes better than 3mm — so it shows that <3mm is a risk factor, not that 3mm specifically is a proven, optimal, or sufficient target for LMM.

Separately, work summarised in Orme & Moncrieff (2024) draws on McKinnon et al.’s analysis of 2,681 Sydney Melanoma Unit patients with melanomas up to 2mm thick. Across the full range of margins, local recurrence fell along a continuous gradient (crude rates 1.06–3.85% by margin band), but when patients with histologic margins under 8mm were excluded from the analysis, margin width stopped predicting recurrence at all — only tumour thickness remained significant. In other words, this looks like a threshold or plateau rather than a straightforward dose-response: risk rises as margins narrow below roughly 8mm (≈1cm surgical margin, assuming 20% shrinkage), then flattens, with no further measurable benefit from wider margins. The same pattern was reported for thicker melanoma, where histologic margins under 16mm (≈2cm surgical) were associated with worse local disease-free survival (a recurrence endpoint, not a mortality one — “local disease-free survival” here means freedom from local recurrence, not death) in melanomas over 4mm thick (HR 2.41, p=0.01) (11). This is a genuine finding from the studies’ own secondary analyses, not just an artefact of where the cutpoint was drawn — though as single-institution retrospective series, “no further benefit beyond the threshold” is suggestive rather than proven, and this remains a useful independent data point rather than a substitute for prospective, subtype-specific studies of histological margin and recurrence.

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