Excision Margins in the Treatment of Primary Cutaneous Melanoma

A Systematic Review of Randomized Controlled Trials Comparing Narrow vs Wide Excision

Marko B. Lens, MD; Martin Dawes, MD; Tim Goodacre, MD; Julia A. Newton Bishop, MD

Background: The optimal excision margin for primary cutaneous melanoma remains controversial, although several clinical studies have suggested that wide local excision is unnecessary.

Hypothesis: Wide excision margins do not improve survival in patients with melanoma.

Objectives: To describe the published evidence and determine the effectiveness of wide surgical margins compared with narrow surgical margins.

Design: Systematic review of randomized controlled trials that compared narrow margins with wide excision margins for cutaneous melanoma.

Setting: Randomized controlled trials available by March 2001.

Subjects: The included trials comprised 2406 participants.

Intervention: Surgical excision of melanoma using narrow excision margins compared with excision using wide excision margins.

Main Outcome Measure: Effect of width of excision margin on melanoma recurrences, disease-free survival, and overall survival.

Results: We identified and analyzed 4 randomized controlled trials. All 4 trials failed to demonstrate statistically significant differences in overall survival and disease-free survival when comparing wide vs narrow excision. Peto pooled odds ratio for overall survival was 0.79 (95% confidence interval, 0.61-1.04) and for disease-free survival was 0.89 (95% confidence interval, 0.69-1.13), indicating a statistically nonsignificant improvement with wide excision.

Conclusions: Not one of the included studies showed any statistically significant difference between the 2 groups treated with narrow or wide excision margins with regard to recurrences and survival. However, current evidence is not sufficient to address the optimal surgical margins for all melanomas, and further research is required.

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IN THE LOCAL TREATMENT of primary cutaneous malignant melanoma, the surgeon’s main goals are to prevent disease recurrences and to promote long-term survival. The secondary aims are to do this with minimal surgical morbidity, short hospital stay, and good cosmetic results. The width of excision margins strongly affects these secondary aims. The optimal excision margin for primary cutaneous melanoma remains controversial.

In 1907, Handley1 published an anecdotal report recommending a liberal resection of skin and considerable amounts of subcutaneous tissue surrounding a cutaneous melanoma on the basis of histologic studies in a single patient with melanoma metastatic to lymph glands. In 1962, Petersen et al2 advocated the need for wide local excision and suggested surgical excision with lateral excision margins of at least 5 cm around the primary tumor. This aggressive approach was considered necessary to prevent local recurrences, but it requires use of skin grafting or flap surgery leading to increased morbidity and, sometimes, unacceptable cosmetic results. The approach was advocated partly as a result of Handley’s report but presumably also as a result of clinicians’ experiences of local and in-transit recurrence. Local recurrence in malignant melanoma is a negative prognostic sign, and its occurrence is associated with generally poor survival and specifically with an increased risk of regional and distant metastasis.3 There have been 2 histopathological studies of melanoma reported in recent years in which the presence of significant residual tumor was shown to be unlikely if...
many surgeons have started to perform resections of cu-
tumors. The necessity for wide excision of thicker tumors
was challenged for thin tumors, and there is a broad
improvement that aggressive surgery is unlikely to have a
the presence of micrometastases in the skin around primary tu-
bers that might better inform choice of excision margins.
When Breslow and Macht introduced the concept that
dogma of wide excision was challenged for thin tumors, and there is a broad
international consensus that 1-cm margins are safe for thin
tumors. The necessity for wide excision of thicker tumors
is 2 cm.

it was not visible in the gross specimen. There has been
no systematic study, however, designed to detect the pres-
ance of micrometastases in the skin around primary tu-
bers that might better inform choice of excision margins.
When Breslow and Macht introduced the concept that
prognosis was related to tumor thickness, the dogma of wide excision was challenged for thin tumors, and there is a broad
tuberculosis technique for surgically removing selected cu-
Tumor Thickness | Excision Margin

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>UK MSG, mm</th>
<th>WHO</th>
<th>Australian</th>
<th>Dutch MSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>2-5 mm</td>
<td>3 mm</td>
<td>2 mm</td>
<td>2 mm</td>
</tr>
<tr>
<td>&lt;1</td>
<td>1 cm</td>
<td>1 cm</td>
<td>1 cm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1-2</td>
<td>1-2 cm</td>
<td>1 cm</td>
<td>1 cm</td>
<td>1 cm</td>
</tr>
<tr>
<td>2-1-4</td>
<td>2-3 cm (2 cm preferred)</td>
<td>2 cm</td>
<td>1 cm</td>
<td>2 cm</td>
</tr>
<tr>
<td>&gt;4</td>
<td>2-3 cm</td>
<td>2 cm</td>
<td>2 cm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

*MSG indicates Melanoma Study Group; WHO, World Health Organization.
†For melanomas thicker than 1.5 mm, recommended excision margin is 2 cm.

We included only randomized controlled trials that compared narrow vs wide excision of primary melanoma. Patients had to have a clinically diagnosed skin melanoma with no evidence of me-
tastases in regional lymph nodes or at distant sites (stages I and
II according to American Joint Committee on Cancer staging criteria). Randomization is the only method available to ensure that both groups are equal in terms of known as well as un-
known confounding variables. Although there are many more pro-
spective studies available that were not randomized, we decided that the bias in these trials for this review was unacceptable.

**SEARCH STRATEGY**

Our aim was to identify all relevant randomized controlled tri-
als that were available for review by March 2001. We con-
ducted sensitive electronic searches of MEDLINE (from 1966
to March 2001), EMBASE (1974 to March 2001), and the Con-
trolled Trials Register from the Cochrane Library (issue 4, 2000), using the recommended Cochrane Collaboration search strategy
with Medical Subject Headings melanoma and excision mar-
gin including all subheadings. We reviewed all relevant articles found in the searches, as well as those of review articles and textbooks. We also hand searched selective conference proceedings. No language restrictions were applied. Where possible, we contacted the authors of the trials to verify the data and obtain additional unpublished data. We contacted ex-

**DATA EXTRACTION AND STUDY APPRAISAL**

We extracted the following data from each study: the random-
ization process including strategy for concealment of alloca-
tion, number of randomized patients, duration of follow-up, and number lost to follow-up.

The main outcome measures were as follows: number of patients with local recurrences as a site of first relapse, the inci-
cidence of other metastases (in-transit metastases, regional me-
tastases, or distant metastases), and overall and disease-free sur-
vival at the end of the follow-up period.

Two reviewers independently extracted the data from each
study, and any disagreements were resolved by discussion.

**STATISTICAL METHODS**

For each trial, we constructed 2 contingency tables enumer-
ing number of participants with outcome event and with-
out outcome event separately for the intervention group (pa-
tients randomized to narrow excision) and control group (pa-
tients randomized to wide excision).

For each outcome of interest, we calculated relative risk reduction with 95% confidence interval (CI), absolute risk reduction with 95% CI, number needed to treat with 95% CI, and odds ratio with 95% CI. For this calculation we used CAT Maker software (available at: http://cebm.jr2.ox.ac.uk).

We calculated the odds ratio and 95% CI for 5-year over-
all survival and 5-year disease-free survival in the patients treated with narrow excision relative to those treated with wide exci-
sion by means of Peto modification of the Mantel-Haenszel
method (using Cochrane Collaboration Review Manager 4.1;
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**METHODS**

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**RESULTS**

**STUDY CHARACTERISTICS**

We retrieved 173 published articles reporting safety of excision margins in the resection of primary melanoma. We identified and analyzed 4 randomized controlled tri-
The main outcome measures were local recurrence, in-transit metastases, regional metastases, distant metastases, overall survival, and disease-free survival (Table 3). A total of 21 patients with local recurrences were recorded (12 in narrow and 9 in wide excision groups). The number of patients with local recurrences varied among trials (in the patients randomized to narrow excision, from 2 to 5; in the wide excision group, from 0 to 6). The difference in local recurrence between patients having wide or narrow excision was not statistically significant in any of the studies.

The definition of local recurrence has varied among studies. In the Intergroup trial, a local recurrence was defined as a pathologically documented melanoma that recurred within 2 cm of the surgical scar. The Swedish study defined local recurrence as a recurrence in the scar or transplant. In the WHO trial, local recurrence was defined as cutaneous or subcutaneous nodules that appeared along the surgical scar or within 1 cm from the scar.

IN-TRANSIT, REGIONAL, AND DISTANT METASTASES

The difference in rate of in-transit, regional, and distant metastases between patients having wide or narrow excision was not statistically significant in any of the studies.

OVERALL SURVIVAL

A total of 1979 live patients were recorded (972 allocated to narrow excision vs 1007 allocated to wide excision). Five-year overall survival data were available for 3 trials, and we therefore pooled the data and performed a meta-analysis (Figure 1). Peto pooled odds ratio was 0.79 (95% CI, 0.61-1.04).

DISEASE-FREE SURVIVAL

Disease-free survival was reported for a total of 1854 patients (905 had narrow excision compared with 949 who had wide excision). We also pooled the data for 5-year disease-free survival for 3 trials and performed a meta-analysis (Figure 2). Peto odds ratio was 0.89 (95% CI, 0.69-1.13).

None of the studies has shown a statistically significant difference between the 2 groups who were treated with narrow or wide excision margins with regard to overall survival.

**Table 2. Characteristics of RCTs Comparing Narrow vs Wide Excision Margins in Surgical Treatment of Primary Melanoma**

<table>
<thead>
<tr>
<th>Trial, Year</th>
<th>No. of Subjects</th>
<th>Narrow Resection Margin, cm</th>
<th>Wide Resection Margin, cm</th>
<th>Tumor Thickness, mm</th>
<th>Tumor Site</th>
<th>Median Length of Follow-up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>French Multicentric Trial, 1993</td>
<td>319</td>
<td>2</td>
<td>5</td>
<td>&lt;2</td>
<td>Trunk, limbs, head and neck</td>
<td>4.2</td>
</tr>
<tr>
<td>Intergroup Melanoma Trial 1996</td>
<td>470</td>
<td>2</td>
<td>4</td>
<td>1-4</td>
<td>Trunk, proximal part of limbs</td>
<td>7.6</td>
</tr>
<tr>
<td>Swedish MSG Trial 1996</td>
<td>989</td>
<td>2</td>
<td>5</td>
<td>0.8-2</td>
<td>Trunk, limbs (except hands and feet)</td>
<td>11</td>
</tr>
<tr>
<td>WHO Melanoma Trial 10, 1991</td>
<td>612</td>
<td>1</td>
<td>3</td>
<td>&lt;2</td>
<td>Trunk, limbs (except fingers and toes)</td>
<td>7.5</td>
</tr>
</tbody>
</table>

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ARR, absolute risk reduction; NNT, number needed to treat; OR, odds ratio; and WHO, World Health Organization.

dent prognostic indicator of survival.3,21

Because the included trials reported the data with different lengths of follow-up, we were not able to pool the data for all events and were restricted to survival outcomes. Furthermore, narrow and wide excision margins were not the same in all trials.

We were unfortunately unable to carry out a meta-analysis on local or in-transit metastases, but this outcome is important. Local recurrence is associated with a poor prognosis but does not appear to be an independent prognostic indicator of survival.3,21

The Intergroup trial showed that the incidence of local recurrence increased 6- to 8-fold in patients with ulcerated melanomas compared with nonulcerated melanomas of intermediate thickness.14

The rate of local recurrences in general is low. Many studies demonstrated that the bulk of local recurrences occur beyond the second year of follow-up. Thus, long-term follow-up is required.

The tumor thickness among the participants of the trial varied. The individual studies included in our systematic review and a meta-analysis of the 3 studies support the view that the excision margin for tumors thinner than 2 mm in Breslow thickness has no effect on disease-free survival or overall survival.

Table 3. Outcome Data of Included Randomized Controlled Trials Comparing Wide Excision vs Narrow Excision Margins in Patients With Malignant Melanoma

<table>
<thead>
<tr>
<th>Event and Trial</th>
<th>CER</th>
<th>EER</th>
<th>RRR (95% CI), %</th>
<th>ARR (95% CI)</th>
<th>NNT (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intergroup Trial</td>
<td>0.026</td>
<td>0.021</td>
<td>19 (–84 to 100)</td>
<td>0.005 (–0.022 to 0.032)</td>
<td>200 (32 to ∞)</td>
<td>0.81 (0.24 to 2.69)</td>
</tr>
<tr>
<td>Swedish Trial</td>
<td>0.010</td>
<td>0.006</td>
<td>40 (–71 to 100)</td>
<td>0.004 (–0.007 to 0.015)</td>
<td>250 (67 to ∞)</td>
<td>0.64 (0.15 to 2.71)</td>
</tr>
<tr>
<td>WHO Trial</td>
<td>0</td>
<td>0.013</td>
<td>∞</td>
<td>–0.013 (–0.026 to 0)</td>
<td>–77 (–3481 to –39)</td>
<td>9.18 (0.49 to 171.24)</td>
</tr>
<tr>
<td>In-transit metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intergroup Trial</td>
<td>0.052</td>
<td>0.059</td>
<td>–13 (–92 to 65)</td>
<td>–0.007 (–0.048 to 0.034)</td>
<td>–143 (30 to ∞)</td>
<td>1.15 (0.52 to 2.53)</td>
</tr>
<tr>
<td>Swedish Trial</td>
<td>0.019</td>
<td>0.040</td>
<td>–111 (–100 to 1)</td>
<td>–0.021 (–0.042 to 0)</td>
<td>–48 (4972 to ∞)</td>
<td>2.09 (0.96 to 4.54)</td>
</tr>
<tr>
<td>WHO Trial</td>
<td>0.007</td>
<td>0.007</td>
<td>0 (–100 to 100)</td>
<td>0 (–0.013 to 0.013)</td>
<td>∞</td>
<td>1.91 (0.14 to 7.19)</td>
</tr>
<tr>
<td>Regional metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intergroup Trial</td>
<td>0.134</td>
<td>0.126</td>
<td>6 (–39 to 51)</td>
<td>0.008 (–0.052 to 0.068)</td>
<td>125 (15 to ∞)</td>
<td>0.94 (0.55 to 1.60)</td>
</tr>
<tr>
<td>Swedish Trial</td>
<td>0.119</td>
<td>0.147</td>
<td>–24 (–59 to 12)</td>
<td>–0.028 (–0.070 to 0.014)</td>
<td>–36 (70 to ∞)</td>
<td>1.28 (0.88 to 1.85)</td>
</tr>
<tr>
<td>WHO Trial</td>
<td>0.078</td>
<td>0.069</td>
<td>12 (–41 to 65)</td>
<td>0.009 (–0.032 to 0.050)</td>
<td>112 (20 to ∞)</td>
<td>0.87 (0.47 to 1.60)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intergroup Trial</td>
<td>0.220</td>
<td>0.261</td>
<td>–19 (–53 to 16)</td>
<td>–0.041 (–0.117 to 0.035)</td>
<td>–25 (29 to ∞)</td>
<td>1.25 (0.82 to 1.91)</td>
</tr>
<tr>
<td>Swedish Trial</td>
<td>0.138</td>
<td>0.149</td>
<td>–8 (–40 to 24)</td>
<td>–0.011 (–0.055 to 0.033)</td>
<td>–9 (31 to ∞)</td>
<td>1.09 (0.76 to 1.56)</td>
</tr>
<tr>
<td>WHO Trial</td>
<td>0.046</td>
<td>0.056</td>
<td>–22 (–98 to 54)</td>
<td>–0.010 (–0.045 to 0.026)</td>
<td>–101 (41 to ∞)</td>
<td>1.24 (0.60 to 2.55)</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Trial at 5 y</td>
<td>0.903</td>
<td>0.928</td>
<td>–3 (–10 to 4)</td>
<td>–0.025 (–0.086 to 0.036)</td>
<td>–4 (28 to ∞)</td>
<td>1.38 (0.62 to 3.07)</td>
</tr>
<tr>
<td>Intergroup Trial at 5 y</td>
<td>0.82</td>
<td>0.76</td>
<td>7 (–1 to 16)</td>
<td>0.060 (0.012 to 0.132)</td>
<td>17 (8 to ∞)</td>
<td>0.70 (0.45 to 1.10)</td>
</tr>
<tr>
<td>Swedish Trial at 10 y</td>
<td>0.76</td>
<td>0.79</td>
<td>–4 (–11 to 3)</td>
<td>–0.030 (–0.082 to 0.022)</td>
<td>–34 (46 to ∞)</td>
<td>1.19 (0.88 to 1.60)</td>
</tr>
<tr>
<td>WHO Trial at 8 y</td>
<td>0.903</td>
<td>0.896</td>
<td>1 (–5 to 6)</td>
<td>0.007 (–0.041 to 0.055)</td>
<td>143 (19 to ∞)</td>
<td>0.92 (0.55 to 1.56)</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>French Trial at 5 y</td>
<td>0.873</td>
<td>0.91</td>
<td>–4 (–12 to 4)</td>
<td>–0.037 (–0.105 to 0.031)</td>
<td>–28 (33 to ∞)</td>
<td>1.44 (0.70 to 2.94)</td>
</tr>
<tr>
<td>Intergroup Trial at 5 y</td>
<td>0.80</td>
<td>0.75</td>
<td>6 (–1 to 16)</td>
<td>0.056 (–0.024 to 0.124)</td>
<td>20 (9 to ∞)</td>
<td>0.75 (0.48 to 1.16)</td>
</tr>
<tr>
<td>Swedish Trial at 10 y</td>
<td>0.70</td>
<td>0.71</td>
<td>–1 (–10 to 7)</td>
<td>–0.010 (–0.067 to 0.047)</td>
<td>–101 (22 to ∞)</td>
<td>1.05 (0.80 to 1.38)</td>
</tr>
<tr>
<td>WHO Trial at 8 y</td>
<td>0.844</td>
<td>0.816</td>
<td>3 (–4 to 10)</td>
<td>0.028 (–0.031 to 0.087)</td>
<td>36 (12 to ∞)</td>
<td>1.44 (0.70 to 2.94)</td>
</tr>
</tbody>
</table>

* CER indicates control event rate (wide excision); EER, experimental event rate (narrow excision); RRR, relative risk reduction; CI, confidence interval; ARR, absolute risk reduction; NNT, number needed to treat; OR, odds ratio; and WHO, World Health Organization.

Comparison: 01 Excision Margins
Outcome: 01 Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Narrow, No./Total No.</th>
<th>Wide, No./Total No.</th>
<th>OR (95% CI Fixed)</th>
<th>Weight, %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>French Trial</td>
<td>142/153</td>
<td>105/166</td>
<td>1 (0.14 to 7.19)</td>
<td>8.8</td>
<td>1.38 (0.62-3.07)</td>
</tr>
<tr>
<td>Intergroup Trial</td>
<td>181/238</td>
<td>190/232</td>
<td>1 (0.14 to 7.19)</td>
<td>39.0</td>
<td>0.70 (0.45-1.10)</td>
</tr>
<tr>
<td>Swedish Trial</td>
<td>409/476</td>
<td>456/513</td>
<td>1 (0.14 to 7.19)</td>
<td>52.3</td>
<td>0.76 (0.52-1.11)</td>
</tr>
<tr>
<td>Total</td>
<td>732/867</td>
<td>796/911</td>
<td>1 (0.14 to 7.19)</td>
<td>100.0</td>
<td>0.79 (0.61-1.04)</td>
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</tbody>
</table>

Test for Heterogeneity χ² = 2.15, P = .34
Test for Overall Effect z = –1.68, P = .09

Figure 1. Effect of excision margins on postoperative 5-year overall survival. OR indicates odds ratio, CI, confidence interval.
Although a 1-cm margin is now widely accepted as adequate for thin (<1 mm thick) melanoma, the minimum margins necessary for thicker lesions (>4 mm) remain unclear. Minimum margins for intermediate-thickness melanoma (1-4 mm) are still disputable. No one trial included only thick melanomas; 3 trials (French, Swedish, and WHO trials) examined melanomas up to 2 mm in thickness, while only 1 trial (Intergroup trial) was conducted on melanomas with thickness up to 4 mm. In the Intergroup trial, 213 patients (43.8% of all randomized patients) had tumors 2 mm or thicker, which represents only 8.9% of all patients from the 4 randomized trials included here. On the basis of this evidence, we do not feel confident to make a strong statement about what margins are acceptable in the 2-mm to 4-mm group, although according to many authors a 2-cm margin is held to be appropriate.

Current evidence including this review provides no guidelines for thick melanomas (>4 mm in thickness), and the optimal treatment for patients with these lesions has not been well established.

Since these tumors have a particularly high recurrence rate (>10%), many surgeons recommend a wider excision margin on the basis of the assumption that better local control might be achieved, while some authors suggest that tumor thickness should not influence surgical margins. The results of the United Kingdom Melanoma Study Group excision trial, which compares 1-cm vs 3-cm margins of excision in patients with melanoma 2 mm or thicker, are awaited.

Trials included in our study do not specifically address the surgical management of several important types of melanoma, and there is no prospective randomized study with data that would establish guidelines for the treatment of in situ melanomas; melanomas on the head, neck, hands, or feet; and melanomas more than 4 mm thick.

Current evidence is not sufficient to address the optimal surgical management for all melanomas, but this meta-analysis provides further evidence that excision margins (in excess of 1 cm) have no effect on disease-free survival or overall survival for melanomas less than 2 mm in thickness. Further research is necessary, and subsequent trials should determine the appropriate local treatment for thick melanoma as well as examine whether narrower margins might be safe in certain types of melanomas and some subgroups of patients.

**Comparison: 01 Excision Margins**

<table>
<thead>
<tr>
<th>Study</th>
<th>Narrow, No./Total No.</th>
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<td>145/166</td>
<td></td>
<td>9.3</td>
<td>1.44 (0.70-2.94)</td>
</tr>
<tr>
<td>Intergroup Trial</td>
<td>178/238</td>
<td>186/232</td>
<td></td>
<td>34.1</td>
<td>0.75 (0.48-1.16)</td>
</tr>
<tr>
<td>Swedish Trial</td>
<td>386/476</td>
<td>426/513</td>
<td></td>
<td>58.6</td>
<td>0.88 (0.63-1.21)</td>
</tr>
<tr>
<td>Total</td>
<td>704/867</td>
<td>757/911</td>
<td></td>
<td>100.0</td>
<td>0.89 (0.69-1.13)</td>
</tr>
</tbody>
</table>

Test for Heterogeneity χ² 2 = 2.32, P = .31
Test for Overall effect z = -0.98, P = .3

**Figure 2.** Effect of excision margins on postoperative 5-year disease-free survival. OR indicates odds ratio; CI, confidence interval.

**REFERENCES**