Excision Margins in the Treatment of Primary Cutaneous Melanoma

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

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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
it was not visible in the gross specimen. There has been no systematic study, however, designed to detect the presence of micrometastases in the skin around primary tumors 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, however, and there is a broad international consensus that 1-cm margins are safe for thin tumors. The necessity for wide excision of thicker tumors that might better inform choice of excision margins.

The currently recommended excision margins for cutaneous melanoma are given in Table 1.

<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>5 mm</td>
<td>5 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>

**Table 1. Currently Recommended Excision Margins for Primary Melanoma**

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

The emerging view is that aggressive surgery is unlikely to have a significant effect on survival and that mutilating surgery should therefore be avoided. In this study, we considered the clinical trial evidence for this view.

We conducted a systematic review of all randomized controlled trials that have examined the resection margins for cutaneous melanoma comparing narrow margins with wide excision margins. This was done to assess the effect of width of excision margin on melanoma recurrences, disease-free survival, and overall survival.

### METHODS

#### INCLUSION CRITERIA

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 metastases 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 unknown confounding variables. Although there are many more prospective 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 trials that were available for review by March 2001. We conducted sensitive electronic searches of MEDLINE (from 1966 to March 2001), EMBASE (1974 to March 2001), and the Controlled Trials Register from the Cochrane Library (issue 4, 2000), using the recommended Cochrane Collaboration search strategy with Medical Subject Headings melanoma and excision margin 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 experts in the field and asked them about any published or unpublished work that they might be aware of.

#### DATA EXTRACTION AND STUDY APPRAISAL

We extracted the following data from each study: the randomization process including strategy for concealment of allocation, 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 incidence of other metastases (in-transit metastases, regional metastases, or distant metastases), and overall and disease-free survival 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 × 2 contingency tables enumerating number of participants with outcome event and without outcome event separately for the intervention group (patients randomized to narrow excision) and control group (patients 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://ceb.m.jr2.ox.ac.uk).

We calculated the odd ratio and 95% CI for 5-year overall survival and 5-year disease-free survival in the patients treated with narrow excision relative to those treated with wide excision by means of Peto modification of the Mantel-Haenszel method (using Cochrane Collaboration Review Manager 4.1; The Nordic Cochrane Center, Copenhagen, Denmark). Heterogeneity between trials was assessed by χ² distribution.

#### RESULTS

We retrieved 173 published articles reporting safety of excision margins in the resection of primary melanoma. We identified and analyzed 4 randomized controlled trials, published in 7 reports from 1988 to April 2001.
No unpublished eligible studies were identified. In some reports, however, not all of the outcome measures were included. Therefore, we asked the investigators to confirm the extracted data and to provide us with the missing data.

Only the Swedish trial and World Health Organization (WHO) Melanoma Trial had sufficient description of study design to suggest that adequate concealment of allocation had taken place; in other trials methods for concealment of allocation were not clear. A total of 2406 patients were randomized in the 4 included trials (1178 patients randomized to narrow excision vs 1228 patients randomized to wide excision).

**FOLLOW-UP**

Follow-up was reported in the Intergroup Melanoma Trial as 92%, but this refers also to a nonrandomized group of patients who joined the prospective study. The last Intergroup publication reported survival in 468 randomized patients (238 patients had a 2-cm margin and 230 patients had a 4-cm margin), which is 96.3% of the patients who entered the study. Karakousis et al reported results with a median follow-up of 91 months on 470 patients (238 had a 2-cm margin and 232 had a 4-cm margin), which is 96.7% of the patients who entered the study originally. Although the last publication stated that the results were reported on the basis of “randomized intent,” it seems that the intention-to-treat analysis was not applied. We tried to contact the authors to obtain confirmation, but no information was obtained.

In the Swedish Melanoma Study Group Trial, only 5 patients (0.5%) were lost to follow-up. The WHO Melanoma Trial 10 did not report the number of patients lost during follow-up in relevant papers. The authors verbally reported that they achieved 100% follow-up.

The main outcome measures were local recurrences, in-transit metastases, regional metastases, distant metastases, overall survival, and disease-free survival (Table 3).

**LOCAL RECURRENCE**

The incidence of local recurrences as a site of first relapse of melanoma was reported in 3 trials including 2071 patients.

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 occurred 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.

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**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>~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, 2000</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>~2</td>
<td>Trunk, limbs (except fingers and toes)</td>
<td>7.5</td>
</tr>
</tbody>
</table>

*RCTs indicates randomized controlled trials; MSG, Melanoma Study Group; and WHO, World Health Organization.*
or disease-free survival. However, in trying to combine data from these studies, we have been faced with significant methodologic problems as well as clinical heterogeneity between the individual studies.

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.21

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.

The 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 (95% CI)</th>
<th>EER (95% CI)</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 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 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>0.062</td>
<td>0.059</td>
<td>-13 (-92 to 65)</td>
<td>-0.007 (-0.048 to 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 013)</td>
<td>∞</td>
<td>1.01 (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 066)</td>
<td>125 (15 to 10)</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 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 050)</td>
<td>112 (20 to 10)</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 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 033)</td>
<td>-91 (31 to 10)</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 025)</td>
<td>-101 (41 to 10)</td>
<td>1.24 (0.60 to 2.35)</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 036)</td>
<td>-4.1 (28 to 10)</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 132)</td>
<td>17 (8 to 10)</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 022)</td>
<td>-34 (46 to 10)</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 055)</td>
<td>143 (19 to 10)</td>
<td>0.92 (0.55 to 1.56)</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Trial at 5 y</td>
<td>0.873</td>
<td>0.91</td>
<td>-4 (-12 to 4)</td>
<td>-0.037 (-0.105 to 031)</td>
<td>-28 (33 to 10)</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 124)</td>
<td>20 (9 to 10)</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 047)</td>
<td>-101 (22 to 10)</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 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.

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.

### References