2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial

Peter Gillgren, Krzysztof T Drzewiecki, Marianne Niin, Hans P Gullestad, Henrik Hellborg, Eva Månsson-Brahme, Christian Ingvar, Ulrik Ringborg

Summary

Background Optimum surgical resection margins for patients with clinical stage IIA–C cutaneous melanoma thicker than 2 mm are controversial. The aim of the study was to test whether survival was different for a wide local excision margin of 2 cm compared with a 4-cm excision margin.

Methods We undertook a randomised controlled trial in nine European centres. Patients with cutaneous melanoma thicker than 2 mm, at clinical stage IIA–C, were allocated to have either a 2-cm or a 4-cm surgical resection margin. Patients were randomised in a 1:1 allocation to one of the two groups and stratified by geographic region. Randomisation was done by sealed envelope or by computer generated lists with permuted blocks. Our primary endpoint was overall survival. The trial was not masked at any stage. Analyses were by intention to treat. Adverse events were not systematically recorded. The study is registered with ClinicalTrials.gov, number NCT01183936.

Findings 936 patients were enrolled from Jan 22, 1992, to May 19, 2004; 465 were randomly allocated to treatment with a 2-cm resection margin, and 471 to receive treatment with a 4-cm resection margin. One patient in each group was lost to follow-up but included in the analysis. After a median follow-up of 6·7 years (IQR 4·3–9·5) 181 patients in the 2-cm margin group and 177 in the 4-cm group had died (hazard ratio 1·05, 95% CI 0·85–1·29; p=0·64). 5-year overall survival was 65% (95% CI 60–69) in the 2-cm group and 65% (40–70) in the 4-cm group (p=0·69).

Interpretation Our findings suggest that a 2-cm resection margin is sufficient and safe for patients with cutaneous melanoma thicker than 2 mm.

Funding Swedish Cancer Society and Stockholm Cancer Society.

Introduction

The incidence of cutaneous melanoma is increasing in Scandinavia and other countries with predominantly white populations. In Sweden the average increase is 4·1% per year for men and 4·2% per year for women.1 Furthermore, the median age of patients diagnosed with a cutaneous melanoma is low compared with other cancers.2,3 Deaths due to cutaneous melanoma have also increased in most light-skinned populations worldwide in the past few decades.4 In the USA, cutaneous melanoma is the second greatest cause of lost productive years owing to cancer.5,6 Surgical resection margins for patients with localised cutaneous melanoma thicker than 2 mm (T3–T4, N0, M0; American Joint Committee on Cancer system stage IIA–IIC) are still controversial.7 Surgery is the key treatment for patients with localised cutaneous melanoma, and the standard procedure is removal of the tumour with a safety margin from the edge of the tumour border. A trade-off exists between a wide excision, with consequent surgical difficulties, and the relapse-risk with a narrow excision, which could compromise disease-free survival or, worse, overall survival. Wide excisions might also lead to bad cosmetic results, lymphoedema, long hospital inpatient stay, frequent need for skin grafts, or complicated skin flap reconstructions. Historically, cutaneous melanoma has been excised with wide resection margins of 5 cm (sometimes extended to 10 cm towards the local lymph node basin). This treatment policy emerged from a recommendation by Handley in 1907 based on the findings of one autopsy.9 Not until more than 60 years later was the wide-excision policy questioned10 but clinical practice did not change until the late 1980s, when studies suggested that narrow excision margins might be appropriate for thin cutaneous melanomas.11,12 This finding was supported by subsequent data from randomised controlled trials.13–18 In 1992—when our trial was started—data on optimum surgical margins for patients with cutaneous melanomas thicker than 2 mm were insufficient, and this uncertainty continues. Authors of a Cochrane meta-analysis concluded that the evidence on which to base a recommendation of surgical resection margin size for patients with thick tumours is weak. Most randomised controlled trials have generated data about treatment of patients with relatively thin tumours; the Intergroup Melanoma Surgical Trial has reported data for patients treated for intermediately thick cutaneous melanomas (1–4 mm),15–18 but most patients had tumours thinner than 2 mm. Only one randomised controlled trial included patients with cutaneous melanoma thicker than 2 mm, comparing a 1-cm with a 3-cm excision margin.19 In Thomas and 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial

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colleagues’ trial,9 900 patients were randomly assigned and the study showed no statistically significant difference in the rate of local recurrence or in overall survival between the two groups, although the 1-cm margin group had more combined locoregional recurrences (p=0.05). These data do not lend support to the use of margins of 2-cm versus 4-cm.

Overall, evidence from randomised controlled trials is inconclusive in identifying the optimum excision margin for patients with cutaneous melanoma thicker than 2 mm. We aimed to test whether overall survival differs with 2-cm and 4-cm excision margins.

Methods

Patients

This trial was launched by the Swedish Melanoma Study Group in cooperation with the Danish Melanoma Group. Patients were enrolled between January, 1992 and May, 2004. Only patients 75 years or younger with a primary cutaneous melanoma thicker than 2 mm and with clinically localised disease on the trunk or upper or lower extremities were eligible. No patients who underwent surgical nodal staging before randomisation were included. We excluded patients with cutaneous melanoma of the hands, foot, head–neck, and anogenital region, and those with a previous cutaneous melanoma. Patients with malignant diseases other than basal cell carcinoma and in-situ cancer of the cervix uteri were also excluded. Patients were recruited from 53 hospitals in Sweden, Denmark, Estonia, and Norway.

Histological diagnosis was by histogenetic type of melanoma,20 level of invasion,21 tumour thickness,22 and presence of ulceration judged by microscopic examination.

Randomisation and masking

Patients were randomly assigned to have either a 2-cm or a 4-cm surgical excision margin in a 1:1, parallel allocation. The physician enrolled the patients after histological confirmation of a cutaneous melanoma thicker than 2 mm. Randomisation was done by telephone call to a randomisation office—six for Sweden and one for each of the other participating countries. Randomisation was done by sealed envelope or by computer generated lists using permuted blocks. Patients were stratified according to geographic region. No part of the trial was masked.

Procedures

The primary excision of the tumour could be done either by an excisional biopsy (margin of 1–3 mm) or with a 2-cm margin if cutaneous melanoma was strongly suspected. Thus, patients could be allocated to receive either no further surgery (those operated on with a 2-cm margin and randomised to the 2-cm group) or to an additional wide local excision with a margin of up to either 2 cm or 4 cm. Surgical excisions were to extend to, or include, the deep fascia. Pathological excision margins were not registered. Radical surgery was to be performed within 8 weeks after the date of diagnosis; for 55 patients (6%; 22 in the 2-cm group, 33 in the 4-cm group), radical surgery was done later than 8 weeks after diagnosis.

Statistical analysis

The primary objective of the study was to assess overall survival. Secondary outcomes were recurrence-free survival and the number of local recurrences. Estimated 5-year survival for the study population was 60%.
initial plan was to recruit 1000 patients for an interim analysis and then continue and add another 1000 patients to be able to perform an equivalency study containing 2000 patients in total. Towards the end of the enrolment period clinical practice started to change at many centres (tumours close to 2-mm thick were routinely excised with small surgical margins) and the inclusion rate abated, therefore enrolment was stopped in 2004 before reaching the initial goal of 1000 patients. The interim analysis was based on the assumption that 500 patients in each treatment group would enable detection of a reduction of survival to 50% with acceptable statistical power (α=0·05, β=10, power=90%). The actual number of patients recruited provides a power of 87% to detect the differences in survival projected in the original power calculation.

The time of an event was measured from the date of randomisation. For calculation of overall survival, the time to death was used, irrespective of cause. Patients who were diagnosed with a second cutaneous melanoma during the study were censored when analysing time to first relapse (recurrence-free survival) but were included in the overall survival analyses. For recurrence-free survival, either time to first cutaneous melanoma relapse or time to cutaneous melanoma-related death was used (whichever occurred first). Randomised patients with a new, non-lethal malignancy other than...
cutaneous melanoma were still included in the study, and if a cutaneous melanoma event occurred it was included in the recurrence-free survival analyses. We also did an analysis of local recurrence-free survival (included in the recurrence-free survival group) but few events were recorded.

For the statistical analyses we used Kaplan-Meier life-table curves and assessed distributional differences with the log rank test. The number of events in each group were compared by univariate Cox regression analyses and known prognostic factors were assessed with multivariate Cox regression analyses. We used the Wilcoxon (Mann-Whitney) test to compare tumour thicknesses between the groups with local recurrences. Analyses were done with Stata (version 10.0).

In accordance with the intention-to-treat principle, patients who deviated from the protocol were included in all analyses. A sensitivity test was performed with and without patients who underwent sentinel node biopsy. Two patients were lost to follow-up due to emigration, one in each allocation arm, and thus censored at that time. Adverse events were not systematically recorded. This study is registered at ClinicalTrials.gov, number NCT01183936.

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had final responsibility for the decision to submit the paper for publication.

Results
Figure 1 shows the trial profile, and table 1 shows baseline characteristics. About 95% of patients approached agreed to take part in the trial. The median age of patients in the 4-cm group was slightly higher than in the 2-cm group. Median tumour thickness was the same in both groups. Protocol deviations occurred in 145 (15%) of included patients (table 2). Patients who did not meet inclusion criteria after randomisation were not excluded from the study. The most common deviation was definitive surgery occurring later than 8 weeks after primary surgery. A sensitivity test detected no difference in any of the results when this patient group (74 in the 2-cm group and 71 in the 4-cm group) was included and excluded. One patient was randomly assigned because of high clinical suspicion of a cutaneous melanoma—ie, before a histological report was completed. Cutaneous melanoma was then ruled out but the patient was included in the analysis. 82 patients underwent sentinel node biopsy. The sensitivity analysis including and excluding these patients showed no difference in any outcome. The median duration of follow-up was 6-7 years (IQR 4.3-9.5) overall, and 11-8 years (9.3-14.8) in the Swedish cohort. The two patients lost to follow-up were censored at that time. These patients were assumed to be alive for the analyses.

Figure 2: Kaplan-Meier curves of overall and recurrence-free survival after 2-cm or 4-cm excision. Median follow-up was 6.7 years (IQR 4.3-9.5) for overall (A) and recurrence-free (B) survival. Overall survival with an extended follow-up (median 11.8 years, IQR 9.3-14.8) was also analysed in a Swedish cohort of 644 patients (C).
The median surgical excision margins were 2·0 cm in the 2-cm group (IQR 2·0–2·5) and 4·0 cm in the 4-cm group (4·0–4·4). 319 (69%) primary sutures were done in the 2-cm group, and 173 (37%) in the 4-cm group. Overall survival of patients who underwent surgery did not differ significantly between the two groups (p=0·34). Furthermore, overall survival did not differ significantly when surgery at 6 weeks or earlier (64%, 95% CI 60–68) and surgery after 6 weeks (69%, 61–76) were compared (p=0·21). Furthermore, overall survival did not differ significantly when surgery at 6 weeks or earlier (64%, 95% CI 60–68) and surgery after 6 weeks (69%, 61–76) were compared (p=0·21). Furthermore, overall survival did not differ significantly when surgery at 6 weeks or earlier (64%, 95% CI 60–68) and surgery after 6 weeks (69%, 61–76) were compared (p=0·21).

Table 4: Multivariate analysis of overall survival and recurrence-free survival

<table>
<thead>
<tr>
<th>Margin of excision*</th>
<th>n</th>
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<th>Recurrence-free survival</th>
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<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>4 cm</td>
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<td>2 cm</td>
<td>459</td>
<td>1·11 (0·90–1·37)</td>
<td>0·32</td>
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<tr>
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<td></td>
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</tr>
<tr>
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<td></td>
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<tr>
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<td>1·42 (1·10–1·82)</td>
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<td>&lt;0·0001</td>
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<td>Site</td>
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<td></td>
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<tr>
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<td>Trunk</td>
<td>560</td>
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<td>Upper extremity</td>
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<td>Thickness</td>
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<td>117</td>
<td>1·12 (0·76–1·65)</td>
<td>0·58</td>
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</table>

*One patient in the 4-cm group and six patients in the 2-cm group were excluded (two head–neck, two no data for tumour thickness, and three unclassifiable ulceration). †Analyses without these cases did not affect the results.

Discussion

We report no significant difference in overall survival, or in the risk of recurrence or death due to melanoma, between 2-cm and 4-cm surgical excision margins for cutaneous melanoma more than 2-mm thick. Furthermore, long-term follow-up of the Swedish patients did not reveal any differences in survival between the groups. No randomised controlled trial of equal size has been done comparing surgical excision margins of 2 cm and 4 cm for patients with cutaneous melanoma thicker than 2 mm (panel). Most international guidelines suggest an...
excision margin of 2–3 cm for thick tumours but evidence supporting this recommendation is scarce.

Authors of a Cochrane meta-analysis from 2009 concluded that a small, non-statistically significant, but potentially important difference in overall survival between the excision margin groups could not be confidently ruled out. However, despite the large number of patients (3297) included in this meta-analysis, the conclusion applies to cutaneous melanoma of all thicknesses and therefore could be unreliable for patients with thick tumours with poor prognosis for three reasons. First, the meta-analysis was based on five randomised patient cohorts presented in 11 papers. Of these cohorts, three were for thin cutaneous melanomas (seven reports), with one cohort (three reports) for intermediate thickness (1–4 mm) lesions. One study included high-risk cutaneous melanomas (thickness >2 mm) but compared a 1-cm margin with a 3-cm margin. Second, about 240 participants in one study in the meta-analysis had tumours thicker than 4 mm and the authors concluded that few data exist on which to base advice for surgical margins in this group of patients. Third, the conclusions for thick cutaneous melanomas were based on an analysis of subgroups. In our report of 936 patients, 270 had thick tumours (>4 mm).

We compared the results of the four randomised trials including patients with cutaneous melanomas thicker than 2 mm (one study) and patients with cutaneous melanomas 1–4 mm thick (three studies), with our data. Thomas and co-workers compared a 1-cm margin with a 3-cm margin for patients with cutaneous melanoma thicker than 2 mm. They reported a 26% increased risk of locoregional recurrence for the 1-cm treatment group (p=0.05), but overall survival was much the same between groups. We noted no difference in recurrence-free survival (ie, all cutaneous melanoma recurrences) in our study. Our data lend support to the hypothesis that a 2-cm surgical margin is safe but a 1-cm margin might be insufficient for patients with a cutaneous melanoma thicker than 2 mm.

In three reports (using the same group of patients) from the Intergroup Study, the investigators included intermediate thickness (1–4 mm) cutaneous melanomas. Patients were recruited from 77 centres worldwide. In the first report (of 486 patients) the investigators concluded that the excision margin could be safely reduced to 2 cm. However, about 213 patients with tumours 2 mm or thicker were included and none had cutaneous melanomas 4 mm or thicker. In our study we included 666 patients with tumours of thickness 2–3.99 mm and 270 patients with tumours 4 mm or thicker. Therefore, we believe that our data suggest that a reduction of the excision margin to 2 cm is safe for patients with cutaneous melanomas thicker than 2 mm.

In the second report, which included 468 patients, the researchers concluded that local recurrence is associated with high mortality and that a 2-cm margin of excision is safe for disease-specific survival and local recurrence rate. The number of patients with tumours thicker than 2 mm was not presented. We defined a local recurrence as in the scar or transplant. Balch and colleagues’ definition included recurrences within 2 cm of the surgical scar. Despite this difference, in the Intergroup Study local recurrence was no higher than 3.8% (compared with 3% in our study) and these patients had a poor outcome, with only 9% survival at 5 years. The patients with a recurrence beyond the scar could have cutaneous melanomas with different biological characteristics, and could therefore be more aggressive. We classified recurrences beyond the scar as regional skin metastases. Local recurrences per se do not have a substantial detrimental effect on survival. The probability of recurrence of cutaneous melanomas 1.5 mm and thicker in the 5 years after a 5-year recurrence-free survival is estimated to be 14% (9% mortality). Our results therefore should be valid for patients with late recurrences because of the length of follow-up.

One could argue that the proportion of protocol deviations (15%) in our study is high and is therefore a limitation. However, Thomas and colleagues reported much the same proportion of deviations (14%). The large number of deviations in both reports might indicate the difficulties of doing large multicentre trials originating in ordinary, daily clinical practice. We believe that this limitation is unlikely to have had a meaningful effect on the results. Interestingly, late surgery had no effect on the outcome for this subgroup compared with the rest of the cohort. The safety of a 2-cm margin compared with a 4-cm margin was not assessed because registration of surgical complications was not included in the protocol, which is another limitation.

Furthermore, unmasked trials have a risk of biases. Follow-up data was obtained during routine health care
by staff (including surgeons) not directly involved in the randomisation, which helps to reduce bias. Additionally, the primary outcome data (for overall survival) is derived from central registries and is therefore not biased.

More patients in the 2-cm group than in the 4-cm group underwent sentinel node biopsy at the time of wide local excision. The reason for this imbalance is unclear. However, a sensitivity test did not show any difference in outcome when this patient group was excluded from the analyses.

A further limitation is that the study was planned as an equivalency trial with 2000 patients to be included, with the hypothesis that treatment groups would not differ. However, because the inclusion rate was much lower than expected, we terminated the trial early. Nevertheless, our study is the largest randomised controlled trial of resection margins for thick melanomas, overall survival was equal in the two groups, and the survival data were not affected by bias; thus, we believe that the main purpose of the trial was achieved and that our results are the best evidence yet about the size of surgical excision margins.

What margins of excision should be recommended for patients with cutaneous melanomas thicker than 2 mm? Current recommendations have little supporting evidence and most international guidelines suggest a 2–3-cm margin for tumours thicker than 2 mm.1,3,11 Surprisingly, no information exists about frequencies of primary closure in three randomised controlled trials14,19,29 that used a 3-cm margin in one of the treatment groups. Closure of a 3-cm resection margin (diameter 6 cm) has obvious difficulties compared with a 2-cm margin (diameter 4 cm). We show that with a surgical margin of 2 cm, the skin can be closed without skin grafting or skin flaps in most cases. The inclusion of results for length of hospital stay and morbidity data would have been useful; however, it has already been shown that hospital stay is longer in patients treated with a 4-cm margin compared with a 2-cm margin.25 Furthermore, complication rates are high in patients treated with split skin grafts compared with primary sutures.26

Our findings lend support to the use of a 2-cm excision margin for cutaneous melanoma 2 mm or thicker. A meta-analysis should be done of all randomised trials of cutaneous melanoma. St Louis, MO, USA: Quality Medical Publishing, 2003: 15–23.


References


Optimum excision margins for melanoma

Despite more than a century of debate, the optimum excision margins for cutaneous melanoma are still unclear. The question is mundane to the uninformed, but to patients and to health-care providers it is of great importance. A wider excision margin might be oncologically safer, but the closure method needed is more often a skin graft or a complex flap, resulting in greater morbidity and increased cost compared with a narrow margin. In one large trial, 46% of patients treated with 4-cm margins had a skin graft compared with only 11% with 2-cm margins.1

100 years ago a 5-cm radial margin was recommended for all patients with melanoma in the hope of reducing the risk of local recurrence and improving overall survival. However, surgeons began selectively to use narrower margins in the late 20th century, and reported low local recurrence rates and no apparent reduction in overall survival. On the basis of this experience, several prospective, randomised controlled trials were done, comparing narrow margins with wide margins in patients with melanomas of more than 1 mm Breslow thickness. Local recurrence rates were very low, and overall survival did not differ significantly.1–7 However, the trials were underpowered to show equivalence. Systematic reviews and meta-analyses were undertaken and also failed to show any statistically significant difference in overall survival.6–8 The authors of a Cochrane review concluded that “current randomised trial evidence is insufficient to address optimal excision margins for primary cutaneous melanoma.”8

Against this background, the trial data reported by Peter Gillgren and colleagues in The Lancet9 are welcome. 936 patients with melanomas thicker than 2 mm were randomly assigned to either a 2-cm or a 4-cm resection margin. In 2004, enrolment was stopped early because of slow patient recruitment. The authors report no significant difference in overall survival (65% in both groups, p=0.69) or recurrence-free survival (56% in both groups, p=0.82) for the two treatments at 5 years. 134 patients died of melanoma (2-cm resection margin group) compared with 138 deaths (4-cm group), giving a hazard ratio of 0.99 (95% CI 0.78–1.26, p=0.95); and there were 194 recurrences (2-cm group) compared with 200 recurrences (4-cm group), hazard ratio 0.98 (95% CI 0.80–1.19, p=0.80). The authors conclude that a 2-cm resection margin is sufficient for patients with melanomas that are 2 mm or thicker. However, these conclusions need to be tempered by the knowledge that the originally planned equivalence trial design had a target accrual of 2000 patients, yet fewer than 1000 were enrolled. Thus, the statistical power required for an equivalence trial was lacking and the study should be classed as an unplanned non-inferiority trial,10,11 which showed that a 2-cm margin was not inferior to a 4-cm margin.

A previous large trial5 compared outcomes for 3-cm versus 1-cm margins, and also noted no significant overall survival benefit with the wide margin. Therefore, the next question to be addressed is whether a 2-cm margin is preferable to a 1-cm margin or whether a 1-cm margin is sufficient and safe. Morbidity and health-care costs could be decreased if a 1-cm margin is equivalent or non-inferior to a 2-cm margin. A proposal for such a large scale, multicentre trial is being developed.

Perhaps of equal importance to resolve the margin width excision issue in patients with melanoma is proper understanding of the inherent tumour biology necessary for a safe excision margin. Assessment of margins with haematoxylin and eosin staining is a relatively crude pathological technique. North and colleagues12 used comparative genomic hybridisation and fluorescent in-situ hybridisation to identify and map genetically
abnormal melanocytes in histopathologically normal epidermis in acral melanoma wide excision specimens. They identified abnormal melanocytes in 84% of 19 cases, extending a mean distance of 6·1 mm from the histologically assessed margin of in-situ melanomas and 4·5 mm from the margin of invasive melanomas. The failure to clear genetically abnormal melanocytes with an adequately wide excision might be the precursor to locoregional recurrence, which in turn could reduce survival. Sophisticated multidisciplinary science may provide the most rational approach to future excision margin recommendations for melanoma patients.

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We declare that we have no conflicts of interest.


