# Long Term Results of a Randomized Study by the Swedish Melanoma Study Group on 2-cm versus 5-cm Resection Margins for Patients with Cutaneous Melanoma with a Tumor Thickness of 0.8–2.0 mm

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**BACKGROUND.** Large, prospective, randomized trials with long term follow-up are required to obtain an unbiased evaluation of the significance of resection margins in patients with cutaneous melanoma.

**METHODS.** The Swedish Melanoma Study Group performed a prospective, randomized, multicenter study of patients with primary melanoma located on trunk or extremities and with a tumor thickness $> 0.8$ mm and $\leq 2$ mm. Patients were allocated randomly to a 2-cm excision margin or a 5-cm excision margin. In total, 989 patients were recruited during the period 1982–1991. The median follow-up was 11 years (range, 7–17 years) for estimation of survival and 8 years (range, 0–17 years) for evaluation of recurrent disease.

**RESULTS.** The crude rate of local recurrence, defined as a recurrence in the scar or transplant, was $< 1\%$ (8 of 989 patients). Twenty percent of the patients (194 of 989 patients) experienced any disease recurrence, and 15% (146 of 989 patients) died of melanoma. There were no statistically significant differences between the two treatment arms. In a multivariate Cox analysis with patients allocated to wide excision as the reference group, the estimated relative hazards for overall survival and recurrence free survival among those allocated to a 2-cm resection margin were 0.96 (95% confidence interval, 0.75–1.24), and 1.02 (95% confidence interval, 0.80–1.30), respectively.

**CONCLUSIONS.** In this long term follow-up study, local recurrences were found to be rare among patients with tumors $> 0.8$ mm thick and $\leq 2.0$ mm thick. No difference in recurrence rate or survival between the two treatment groups was found. Patients in this category can be treated with a resection margin of 2 cm as safely as with a resection margin of 5 cm. ***Cancer* 2000;89:1495–501.**


**KEYWORDS: primary melanoma, resection margins, tumor thickness 0.8–2 mm, randomized study, long term follow-up, locoregional recurrence, survival.**

The world-wide, upward incidence trend for cutaneous malignant melanoma has led to increasing numbers of patients who need surgical treatment. If the extent of surgery can be reduced without compromising the survival of the patient, then both society and the patients will benefit. Traditionally, large surgical margins were recommended based on observational findings.[1,2] Over the last century, the recommended resection margins have become more narrow.[3,4] A few randomized studies comparing different excision margins for primary tumors of different thicknesses have been performed.[5,6] None of those studies demonstrated any impact on disease recurrence or patient survival with regard to the type of surgery performed.

The Swedish Melanoma Study Group organized a national, multiinstitutional, prospective, randomized study in 1982, randomizing patients with melanoma with a tumor thickness of $> 0.8$ mm and $\leq 2$ mm to receive either a 2-cm excision margin or a 5-cm excision margin. The first report, with a median follow-up of 5.8 years for survival and a 4-year follow-up for evaluation of recurrent disease, was presented in 1996.[7] The conclusion was that treatment results were similar regardless of the size of the excision margin. However, because late events in melanoma may occur,[8–10] a long term follow-up was considered to be warranted. This report presents an update of the Swedish trial, now with a median follow-up for survival of 11 years.

## MATERIALS AND METHODS

### Inclusion and Exclusion Criteria

Patients who met the inclusion criteria had histologically proven, cutaneous, malignant melanoma measuring $> 0.8$ mm and $\leq 2.0$ mm in thickness with a trunk or extremity location (except hands and feet). Patients with melanoma satellites or metastatic disease, however, were not eligible, nor were patients with previous malignant disease (except basal carcinoma). Definite surgical treatment was to be performed within 6 weeks of the primary diagnostic procedure.

### Randomization Technique

Patients were recruited from five geographic areas in Sweden and were allocated randomly by telephone at five regional oncologic centers. The random allocation to the two treatment groups was done using balanced lists. At three of the trial centers, separate lists for each participating hospital were used. At the remaining two centers, there was no stratification by hospital. The personal data of each randomized patient and the tumor thickness were noted on the list before the assigned treatment was revealed. In all, 39 clinics (38 hospitals) recruited patients.

### Treatment

Patients were assigned randomly to either a wide excision with a total resection margin of at least 5 cm or a resection margin of 2 cm. Total resection margin means that, if the tumor primarily was resected with a 2-cm margin and, thus, the patient was randomized to the small excision group, then no further excision was necessitated. However, if the patient was randomized to the 5-cm excision margin group, then a complementary resection of at least 3 cm was performed. Excisions extended to or included the muscular fascia. The reported excision margin is the summarized excision margins for each patient, when available.

### Follow-Up

Patients were scheduled for a clinical follow-up visit every 3 months for 3 years and thereafter every 6 months for 2 years. After 5 years, patients were followed according to local tradition. The standard salvage treatment after locoregional disease recurrence was surgery. After repeated locoregional recurrences, some patients were treated with limb perfusion. In the event of distant dissemination, chemotherapy was given at the discretion of the respective physician. Clinical follow-up information was obtained through the clinical records. The identification of previous and secondary tumors was done by a search of the files of the Swedish National Cancer Registry. Information on vital status was checked against the Swedish Cause-of-Death Registry. The end date for follow-up was November 15, 1998. This implies that the end date for follow-up of overall survival (OS) was common to all patients, whereas the end date for clinical follow-up was the last registered visit. However, five patients were lost to follow-up prior to death due to emigration (1–4 years after primary treatment).

From February 1, 1982 until April 30, 1991, a total of 989 patients were randomized. The protocol, including informed consent, was approved by the ethical review committee of the Karolinska Institute, Stockholm, Sweden.

### Statistics

The primary end point of the trial was survival. Secondary end points were recurrence free survival (RFS) as well as local and regional disease recurrence.

The OS times were calculated from the date of randomization to the date of death, the date of emigration (five patients), or the end date for follow-up (November 15, 1998). The RFS times were calculated from the date of randomization to the date of locore-

gional recurrence, distant metastases, second primary melanoma, or intercurrent death (whichever came first), or, in the absence of an event, to the date of emigration or the end of follow-up.

When analyzing the different types of first events, patients were considered to be at risk of the studied event until the first of the events defining recurrent disease occurred or, in the absence of an event, until the end of follow-up. The occurrence of any other event was treated as a censored observation at the time of its occurrence. The OS and RFS rates were estimated using the Kaplan–Meier method. Distributional comparisons were made using a two-tailed log rank test.[11,12]

Hazards rate ratios and 95% confidence intervals were estimated using the Cox proportional hazards regression model, stratified by region, with wide excision as the reference group.[13] All analyses were based on "intention to treat" and were performed separately for all randomized patients (n = 989 patients) as well as for all eligible patients (n = 895 patients). In the analysis of the eligible patients, potential confounding from other well-documented risk factors, such as gender, age (< 40 years, 40–59 years, and ≥ 60 years), and tumor thickness (< 1.0 mm, 1.0–1.4 mm, and ≥ 1.5 mm) was studied by including these factors, as well as treatment, in the regression models.

## RESULTS

In all, 989 patients were randomized: 476 patients to the group with narrow excision margins and 513 patients to the group with wide excision margins. The median ages were 52 years and 51 years among those who were randomized to narrow or wide excision margins, respectively. The median resection margin in the narrow excision group was 2 cm (range, 0.2–5.5 cm), and it was 5 cm (range, 0.2–10.0 cm) in the wide excision group (mean resection margin, 2.1 cm vs. 4.6 cm). Seventy-five percent of the patients in each treatment group were treated with the exact allocated excision margin. The median tumor thickness was 1.2 mm. Both patient and tumor characteristics were distributed equally among the treatment arms (Table 1). Ulceration of the primary tumor, which was recorded systematically only in the Stockholm-Gotland region (n = 397 patients), also was distributed equally among the treatment arms with the presence of ulceration in 17% of the tumors.

A total of 94 of 989 randomized patients were found to be ineligible according to the inclusion and exclusion criteria (Table 2). The most common reason for ineligibility was a previous cancer diagnosis. From a search of the files of the Swedish National Cancer Registry, we identified the 46 patients who had a diagnosis of another malignancy preceding the date of randomization. Ineligible patients were distributed equally among the two resection groups (Table 2).

The median follow-up was 11 years (range, 7–17 years) for OS. For analysis of RFS, the median follow-up was 8 years (range, 0–17 years). The follow-up times were identical for the two treatment groups.

There was a total of only eight reported incidents of local recurrences (1%), and there were 29 incidents of in-transit metastases reported (3%). Fourteen per-

**TABLE 1**
**Distribution of Patient and Tumor Characteristics**

| Characteristic | Narrow excision (n = 476 patients) | Wide excision (n = 513 patients) |
|---|---|---|
| Age (yrs) | | |
| Median (male/female) | 52 (54/50) | 51 (55/47) |
| Minimum–maximum | 16–81 | 16–84 |
| Tumor thickness (mm) | | |
| Median | 1.2 | 1.2 |
| Minimum–maximum | 0.4–2.9 | 0.3–2.0 |
| Margin of excision (cm) | | |
| Median (%) | 2.0 | 5.0 |
| < 2/< 5 | 57 (12) | 106 (21) |
| 2/5 | 357 (75) | 377 (73) |
| > 2/> 5 | 61 (13) | 27 (5) |
| Data unavailable | 1 (0.2) | 3 (1) |
| Gender (%) | | |
| Male | 225 (47) | 246 (48) |
| Female | 251 (53) | 267 (52) |
| Tumor site (%) | | |
| Trunk | 265 (56) | 282 (55) |
| Lower extremity | 140 (29) | 150 (29) |
| Upper extremity | 61 (13) | 75 (15) |
| Head-neck | 6 (1) | 3 (0.4) |
| Hand | 2 (0.4) | 1 (0.2) |
| Foot | 2 (0.4) | 2 (0.4) |
| Histogenetic type of melanoma (%) | | |
| Superficial spreading melanoma | 371 (78) | 404 (79) |
| Nodular melanoma | 63 (13) | 67 (13) |
| Lentigo maligna melanoma | 0 (—) | 4 (1) |
| Acral lentiginous melanoma | 4 (1) | 2 (0.4) |
| Unclassifiable melanoma | 21 (4) | 18 (4) |
| Melanoma in situ | 0 (—) | 1 (0.2) |
| Data unavailable | 17 (4) | 17 (3) |
| Clark level of invasion (%) | | |
| I | 0 (—) | 1 (0.2) |
| II | 53 (11) | 80 (16) |
| III | 297 (62) | 304 (59) |
| IV | 114 (24) | 120 (23) |
| V | 1 (0.2) | 0 (—) |
| Data unavailable | 11 (2) | 8 (2) |
| Ulceration (%)[a] | | |
| Present | 36 (18) | 33 (17) |
| Absent | 153 (78) | 158 (79) |
| Data unavailable | 8 (4) | 9 (5) |

[a] Ulceration data were available for patients randomized in the Stockholm-Gotland region (narrow excision, n = 197 patients; wide excision, n = 200 patients).

**TABLE 2**
**Cause of Ineligibility**

| Cause | Narrow excision (n = 476 patients) | Wide excision (n = 513 patients) |
|---|---|---|
| Previous malignancy | 24 | 22 |
| Melanoma | 6 | 4 |
| Other cancer | 18 | 18 |
| Not melanoma | 4 | 4 |
| Incorrect tumor site (foot, hand, head-neck) | 10 | 6 |
| Incorrect tumor thickness (mm) | 5 | 9 |
| < 0.8 | 4 | 9 |
| > 2.0 | 1 | 0 |
| Not Stage I or satellites present | 7 | 3 |
| Total no. of ineligible patients (%) | 50 (11) | 44 (9) |

**TABLE 3**
**Total Number of Events by Allocated Treatment**

| Type of event | Narrow excision (n = 476 patients) (%) | Wide excision (n = 513 patients) (%) |
|---|---|---|
| Local recurrence | 3 (0.6) | 5 (1) |
| Regional skin metastasis | 19 (4) | 10 (2) |
| Regional lymph node recurrence | 70 (15) | 61 (12) |
| Distant metastasis | 71 (15) | 71 (14) |
| Any recurrence | 98 (21) | 96 (19) |
| New melanoma | 12 (3) | 9 (2) |
| Death | 117 (25) | 134 (26) |
| Death due to melanoma | 77 (16) | 69 (13) |
| Nonmelanoma death | 40 (8) | 65 (13) |
| Other malignancy | 15 (3) | 28 (5) |
| Cardiovascular | 17 (4) | 26 (5) |
| Other cause of death | 8 (2) | 11 (2) |

cent of patients (142 of 989 patients) were reported to have distant metastases, whereas 15% of patients (146 of 989 patients) died of melanoma (Table 3).

Less than 1% of the patients (5 of 989 patients) had a local recurrence as a first event (Table 4). There was only one local recurrence as first event among those patients who were treated with narrow excision margins, and there were four local recurrences among those patients who were treated with wide excision margins. Four of the five patients with a local recurrence as a first event died of melanoma at a median time of 11 months(range, from 8 months to 3 years) after the diagnosis of the local recurrence. One patient who was treated with a 2-cm excision margin was alive and well 13 years after the first local recurrence. Also, the number of in-transit metastases were few, with no statistically significant difference among the two treatment groups. A second primary melanoma was more common than a local recurrence as the first event. In the Cox multivariate analysis of first events, with wide excision margins as the reference group, no difference between the treatment groups was found. The estimated relative hazard rates for OS and RFS among those patients who were allocated the a 2-cm excision margin group were 0.96 (95% confidence interval, 0.75–1.24) and 1.02 (95% confidence interval, 0.80–1.30), respectively. The evaluations were made for both the 989 randomized patients who were stratified by region and the 895 eligible patients only, with nearly identical results (data not shown). Including major covariates in the Cox regression model in the analyses of first events did not change the results.

The estimated OS at 10 years for the narrow excision margin group was 79% (95% confidence interval, 75–82%) compared with 76% (95% confidence interval, 72–80%) for the wide excision group: That is, there was no statistically significant difference between the treatment groups (Fig. 1). Similarly, there was no statistically significant difference in RFS rates, with a 5-year estimate of 81% (95% confidence interval, 77–84%) for the narrow excision margin group and 83% (95% confidence interval, 80–86%) for the wide excision margin group. The 10-year estimates were 71% (95% confidence interval, 66–75%) versus 70% (95% confidence interval, 65–74%), respectively (Fig. 2). All analyses were on an intent-to treat basis; however, separate analyses also were done excluding the ineligible patients, leading to identical conclusions (data not shown).

## DISCUSSION

The long term results of this national, multiinstitutional study on 989 randomized melanoma patients with a tumor thickness $> 0.8$ mm and $\leq 2.0$ mm showed that this category of patients can be treated with a resection margin of 2 cm as safely as with a resection margin of 5 cm. Thus, we were able to confirm the early results of this study.[7]

Local recurrence, defined as a recurrence in the scar or transplant, was rare, and was not more common among patients who were treated with resection margins of 2 cm compared with those patients who were treated with resection margins of 5 cm. The results with regard to OS and RFS were similar in both treatment groups, in accordance with the early observations. With the extended follow-up, however, from the earlier 5.8 years for estimation of survival now reaching 11 years, and the earlier 4 years for evaluation of recurrent disease compared with 8 years in this analysis, there was an increase in the proportion of events. The incidence of metastases to regional lymph nodes as well as to distant sites and melanoma death increased with time. These findings confirm the need

**TABLE 4**
**Analysis of First Events**

| Type of event | Narrow excision (n = 476 patients) (%) | Wide excision (n = 513 patients) (%) | Relative hazards (95% confidence interval)[a] | *P* value |
|---|---|---|---|---|
| Survival | | | | |
| All deaths | 117 (25) | 134 (26) | 0.96 (0.75–1.24) | 0.77 |
| Melanoma deaths | 77 (16) | 69 (13) | 1.22 (0.88–1.69) | 0.24 |
| Nonmelanoma deaths | 40 (8) | 65 (13) | 0.69 (0.46–1.02) | 0.06 |
| Recurrent disease | | | | |
| Any event | 127 (27) | 135 (26) | 1.02 (0.80–1.30) | 0.88 |
| Locoregional recurrence | 70 (15) | 61 (12) | 1.24 (0.88–1.75) | 0.22 |
| Local recurrence | 1 (0.2) | 4 (1) | | |
| Regional skin metastasis | 6 (1) | 3 (1) | | |
| Regional lymph node metastasis | 63 (13) | 54 (11) | | |
| Distant metastasis | 24 (5) | 34 (7) | 0.76 (0.45–1.28) | 0.29 |
| New primary melanoma | 12 (3) | 9 (2) | 1.42 (0.59–3.40) | 0.43 |
| Intercurrent death | 21 (4) | 31 (6) | 0.75 (0.43–1.30) | 0.31 |

[a] Narrow group versus wide excision group stratified by region.

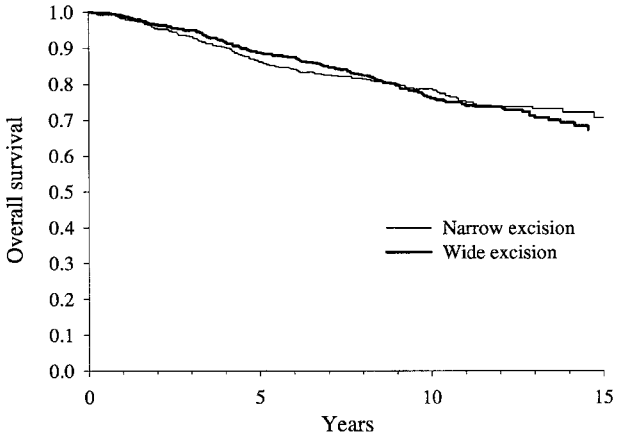


**FIGURE 1.** Overall survival of patients who underwent narrow excision (n = 476 patients) or wide excision (n = 513 patients).

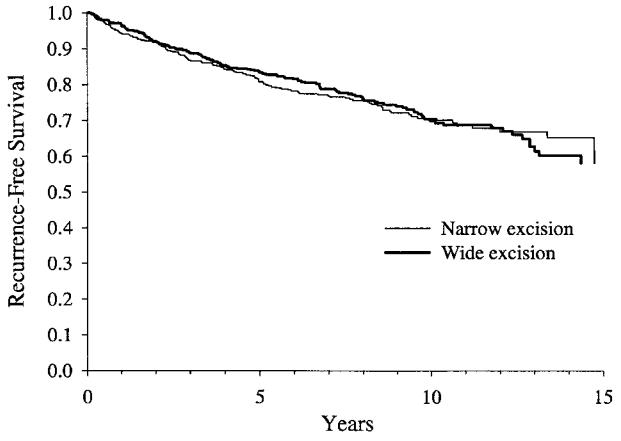


**FIGURE 2.** Recurrence free survival of patients who underwent narrow excision (n = 476 patients) or wide excision (n = 513 patients).

for long term follow-up, which is in accordance with the study by Slingluff et al.[14]

No specific cause of death was found to be overrepresented in the two treatment groups. The proportions of patients dying from other malignant disease, cardiovascular disease, or other causes were distributed equally. Therefore, we believe that the most plausible reason for the somewhat higher number of intercurrent deaths in the wide excision margin group was chance variation.

There is no reason to believe that the choice of salvage treatment was influenced by the allocated excision margin for the primary tumor. In addition, there is no curative treatment available for disseminated malignant melanoma.

Three other major, randomized studies with long term follow-up on the significance of surgical margins in the outcome of patients with cutaneous melanoma have been published to date.[6,15,16] These studies included melanomas of somewhat overlapping tumor thicknesses as well as different resection margins. In the World Health Organization (WHO) study,[6] which had a mean follow-up of 8 years, 612 patients up to the age of 65 years with tumors no thicker than 2 mm that were located on trunk and extremities were included, with the majority (58%) of the tumors $< 1$ mm thick. The resection margins were 1 cm or 3 cm. In the Intergroup Melanoma Surgical Trial, which was presented by Karakousis et al.[15] and Balch et al. (abstract presenting 10-year survival rates)[16] and also was multiinstitutional and had a long term follow-up (91 months), 470 randomized patients were included with melanomas 1–4 mm thick that were located on the trunk or the proximal extremities with resection mar-

gins of 2 cm or 4 cm. None of these studies was able to demonstrate any statistically significant difference between the groups who were treated with narrow or wide excision margins with regard to local recurrence or survival.

The Swedish trial was designed to study the effects of the resection margin on patients of all ages with tumors of $> 0.8$ mm and $\leq 2.0$ mm in thickness. No subgroup analyses with regard to tumor thickness were planned or undertaken, and the question of whether a 1-cm margin is sufficient for patients with melanomas up to 1 mm thick was not addressed by the trial. The WHO trial[6] performed subgroup analyses on OS and RFS, with equal results for patients with tumors that were 0.1–1.0 mm thick versus 1.1–2.0 mm thick. However, because the four events of local recurrence were found among patients with primary tumors that were 1.1–2.0 mm thick, the treatment recommendations on their behalf was 1-cm resection margin only for patients with tumors that were 0.1–1.0 mm thick. Thus, putting data together from these trials shows that a 1-cm excision margin is adequate for patients with melanomas up to 1 mm thick.

The appearance of local recurrence from melanoma has generally been considered a negative prognostic sign.[17] The definition of local recurrence, however, has varied.[18] In the WHO study,[6] a local recurrence was defined as a first recurrence in the scar or within 1 cm of the scar. In the Intergroup study first reported by Balch et al.,[5] local recurrence was defined as recurrence within 2 cm of the scar. It was not expressed whether or not it was always a first recurrence. In Sweden, local recurrence from melanoma is defined as recurrence in the scar or transplant. In a Swedish population-based study on outcomes of patients with local recurrence of cutaneous malignant melanoma, it was concluded that local recurrences as first events were rare (1.3%). The prognostic impact of local recurrence was assessed in a regression model with local recurrence as a time dependent covariate and with consideration of well-documented risk factors. No major detrimental impact from local recurrence on survival was demonstrated.[18] The numbers of local recurrences as a first event in the Swedish randomized surgical trial were few (n = 5 patients), which also was the case in the Intergroup trial among patients with corresponding tumor thickness (n = 3 patients) as well as in the WHO study (n = 4 patients). Likewise, the rate of in-transit metastasis was low, with no difference between the treatment arms in any of the studies.[6,15] From these data, with regard to surgical margins, it is not possible to determine whether local recurrences are potentially dangerous. However, they are a small problem compared with the observed frequency of distant metastasis (Table 3). Because of the few numbers of local recurrences and in-transit metastases as first events, the results probably would not have been any different if the Swedish study had used the same definition for local recurrence that was used in the above-mentioned studies. The prognosis for the patients is more likely to be decided by the biologic properties of the melanoma.

This long term follow-up of 989 randomized patients with malignant melanoma showed that local recurrences are rare among patients with tumors $> 0.8$ mm thick and $\leq 2.0$ mm thick. No difference in disease recurrence rates or OS between the group with 2-cm resection margins and the group with 5-cm resection margins was found. This study has shown that patients with malignant melanoma in this category can be treated with a resection margin of 2 cm as safely as with a resection margin of 5 cm.

## REFERENCES


1. Handley WS. The pathology of melanotic growths in relation to their operative treatment. *Lancet* 1907;1:927–33,96–1003.
2. Petersen NC, Bodenham DC, Lloyd OC. Malignant melanomas of the skin. *Br J Plast Surg* 1962;15:49.
3. Green MS. The changing controversy over surgical resection margins for stage I cutaneous melanoma. *Mount Sinai J Med* 1991;58:341–6.
4. Ross MI. Prospective randomized trials in melanoma: defining contemporary surgical roles. *Cancer Treat Res* 1997;90: 1–27.
5. Balch CM, Urist MM, Karakousis CP, Smith TJ, Temple WJ, Drzewiecki K, et al. Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial. *Ann Surg* 1993; 218:262–9.
6. Veronesi U, Cascinelli N. Narrow excision (1-cm margin): a safe procedure for thin cutaneous melanoma. *Arch Surg* 1991;126:438–41.
7. Ringborg U, Andersson R, Eldh J, Glaumann B, Hafstrom L, Jacobsson S, et al. Resection margins of 2 versus 5 cm for cutaneous malignant melanoma with a tumor thickness of 0.8 to 2.0 mm. *Cancer* 1996;77:1809–14.
8. Reintgen DS, Cox C, Slingluff CLJ, Seigler HF. Recurrent malignant melanoma. The identification of prognostic factors to predict survival. *Ann Plast Surg* 1992;28:45–9.
9. Milton GW, Shaw HM, Farago GA, McCarthy WH. Tumour thickness and the site and time of first recurrence in cutaneous malignant melanoma (Stage I). *Br J Surg* 1980;67: 543–6.
10. Shaw HM, Rivers JK, McCarthy SW, McCarthy WH. Cutaneous melanomas exhibiting unusual biologic behavior. *World J Surg* 1992;16:196–202.
11. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585-612.
12. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1–39.

13. Cox DR. Regression models and life-tables. *J R Stat Soc B* 1972;34:187–220.
14. Slingluff CLJ, Dodge RK, Stanley WE, Seigler HF. The annual risk of melanoma progression. Implications for the concept of cure. *Cancer* 1992;70:1917–27.
15. Karakousis CP, Balch CM, Urist MM, Ross MM, Smith TJ, Bartolucci AA. Local recurrence in malignant melanoma: long-term results of the multiinstitutional randomized surgical trial. *Ann Surg Oncol* 1996;3:446–52.
16. Balch CM, Soong S-J, Intergroup Melanoma Committee. Long-term results of a prospective surgical trial comparing excision margins for patients with 1–4 mm melanomas [abstract no. 59].The Society of Surgical Oncology, New Orleans, March 16–19. 2000:23.
17. Ames FC, Balch CM, Reintgen D. Local recurrences and their management. In: Balch CM, Houghton AN, Milton GW, Sober AJ, Soong S-J, editors. Cutaneous melanoma, 2nd ed. Philadelphia: JB Lippincott Company, 1992;287–94.
18. Cohn-Cedermark G, Månsson-Brahme E, Rutqvist LE, Larsson O, Singnomklao T, Ringborg U. Outcomes of patients with local recurrence of cutaneous malignant melanoma. A population-based study. *Cancer* 1997;80:1418–25.