Stockholm May 9, 2011

Partial translation of the original trial protocol for the submitted D-11-03099 study.

Evaluation of the significance of margins of resection for survival and recurrence in patients with malignant cutaneous melanoma of ≥ 2.1 mm thickness

A Scandinavian multicentre study

September 1990

Group members

As in original protocol.

Introduction

The group summarizes the knowledge at that time.

Key sentences:

The significance of surgical margins of excision has not been studied in a satisfying way.

An analysis of the WHO Melanoma Group registry has not proven that the width of excision is correlated to survival.

……..results indicates that thin malignant melanomas can be excised with a more narrow margin than what is presently used.

Tumours ≤2.0 mm thick has been studied in the WHO melanoma study group comparing a narrow (1–cm) with a wide (3-cm) excision (ref.). No difference was found between the treatment arms.

The Swedish melanoma study group is presently finishing a manuscript in a study that compares a large (5-cm) and narrow (2-cm) excision of malignant melanoma >0.8mm - ≤2.0mm, preliminary data shows no significant difference between the treatment arms.

With the starting point in these studies we find it called for to start a new study including melanoma of ≥2mm thickness.

Aim

To evaluate if the traditional large excision can be changed to a more narrow excision for patients with malignant melanoma of ≥2mm thickness.
Patients will be randomized in two groups:

1. Excision of the tumour with a 2-cm margin.
2. Excision of the tumour with a 4-cm margin.

Primary endpoint is to evaluate survival

Secondary endpoint is to evaluate the frequency of local recurrences and recurrence free survival.

Inclusion criteria

Patients with cutaneous melanoma with thickness ≥2mm, in clinical stage I and ≤ 75 years of age.

Patients with malignant melanoma, that has been operated on with a narrow margin shall, within six weeks undergo radical surgery.

The patients must be fit for surgery.

The patient should be informed and should accept participation in the study.

Exclusion criteria

Patients with malignant melanoma of the hand, feet, head-neck and ano-genital region.

The presence of satellite tumours, so called “in-transit”-tumours (skin metastasises between the primary tumour and the regional lymph node basin), regional or general metastasises.

Other condition that contradicts surgical treatment.

Previous history of cancer (except basal cell carcinoma and cancer in situ colli uteri).

Flowchart

Excision biopsy (at a high melanoma suspicion a 2-cm margin at once)

Histopathology

Randomization

Large excision = re-excision to a total of 4-cm margin / Small excision = no further treatment or re-excision to a total of 2-cm margin.

Definitive surgery should be performed within 6 weeks.

Surgical treatment

The common surgical technique is described. Surgical excision was to extend to, or include, the deep fascia. It is noted that the 4-cm margin of excision commonly will require split skin grafting.

Procedure for the technical process in preparation of the specimen

The procedure is described.

Histological classification

The classification is described

Randomization

In the randomization the patients are allocated to one of the following groups:

a. Group with a small excision
b. Group with a large excision

The data will be stratified according to geographical region and tumour thickness (2,1 mm-3,0mm; ≥3,1mm)

Trial profile

All cases where the diagnosis malignant melanoma is established and where there are no exclusion criterias should participate in the study. Eligible patients who are not included should be registered.
Patients who are randomized can not be excluded.

The randomization is conducted in the separate regions. Thru a telephone call the patient is randomized when the histopathological diagnosis is confirmed. At the time of randomization the following data should be presented; hospital, date of birth, name, day of surgery and tumour thickness.

The regional randomization centres are presented.

Follow-up

Controls after surgical treatment is to be performed every 3:rd month under two years and every 6:th month up until five years. Later follow-up data is collected from local registries.

Evaluation

Primary endpoint: Survival

Secondary endpoint: Local recurrences and disease free survival. A local recurrence is defined as tumour growth is the scar. Recurrences in the skin outside the scar will be registered as in-transit metastasis.

Statistics

The study population has an estimated 5-year survival of 60%. In order to have reasonable chances of statistical significance and power to be able to measure a reduction to 50%, at least 500 patients in each treatment arm is required.

Due to the fact that this study hypothesises that the tested methods of treatment do not differ, the aim is to present a confidence interval as narrow as possible concerning the hypothesised differences between the methods. From this point of view it would be desirable with an even larger cohort, tentatively a thousand patients in each group. The confidence interval for possible differences in the proportion of 5-year survivors will then be in the estimate of +/- 4%.

Between three- and four hundred patients per year can be estimated to fulfil the inclusion criteria to the proposed study. During the first three-year period one should be able to include 500+500 patients. At this point an interim analysis should be performed. If the study – at that time – is continued one should aim for the goal of 1000+1000 patients.

At the time of the first interim analysis after the first three-year period survival analyses should be performed partly with reference to time to recurrence, partly the frequency of local recurrences. If a 1% significance is achieved in either of these analysis a discontinuation of the study should be considerated. This decision should be made by a committee of one representative from each country and a statistician. If the study is continued, the results from the interim analysis should not be spread outside the committee.

The study is discontinued after three + three years, where after the data should be analysed for survival, recurrence free survival and frequency of local recurrences. Data concerning the patients then should be continuously be collected where after a definitive analysis can be performed when the median follow-up time reaches 5 years.

Ethic evaluation

The protocol can be applied first after the ethical committees in each country have given approvals.

The information to the patients should follow the prevailing routines I each country.

Publication

The principal investigator of each centre participating in the study should be a co-author. The study should be published as a whole – and not in separate reports.

References

As in original protocol

Figure

As in original protocol, describing the technique in measuring excision margins at surgery.