Surgical excision margins for primary cutaneous melanoma (Review)

Sladden MJ, Balch C, Barzilai DA, Berg D, Freiman A, Handiside T, Hollis S, Lens MB, Thompson JF

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[Intervention Review]

Surgical excision margins for primary cutaneous melanoma

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ABSTRACT

Background

Cutaneous melanoma accounts for 75% of skin cancer deaths. Standard treatment is surgical excision with a safety margin some distance from the borders of the primary tumour. The purpose of the safety margin is to remove both the complete primary tumour and any melanoma cells that might have spread into the surrounding skin.

Excision margins are important because there could be trade-off between a better cosmetic result but poorer long-term survival if margins become too narrow. The optimal width of excision margins remains unclear. This uncertainty warrants systematic review.

Objectives

To assess the effects of different excision margins for primary cutaneous melanoma.

Search strategy

In August 2009 we searched for relevant randomised trials in the Cochrane Skin Group Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 3, 2009), MEDLINE, EMBASE, LILACS, and other databases including Ongoing Trials Registers.

Selection criteria

We considered all randomised controlled trials (RCTs) of surgical excision of melanoma comparing different width excision margins.

Data collection and analysis

We assessed trial quality, and extracted and analysed data on survival and recurrence. We collected adverse effects information from included trials.

Main results

We identified five trials. There were 1633 participants in the narrow excision margin group and 1664 in the wide excision margin group. Narrow margin definition ranged from 1 to 2 cm; wide margins ranged from 3 to 5 cm. Median follow-up ranged from 5 to 16 years.

Authors' conclusions

This systematic review summarises the evidence regarding width of excision margins for primary cutaneous melanoma. None of the five published trials, nor our meta-analysis, showed a statistically significant difference in overall survival between narrow or wide excision.

The summary estimate for overall survival favoured wide excision by a small degree [Hazard Ratio 1.04; 95% confidence interval 0.95 to 1.15; P = 0.40], but the result was not significantly different. This result is compatible with both a 5% relative reduction in overall mortality favouring narrower excision and a 15% relative reduction in overall mortality favouring wider excision. Therefore, a small (but potentially important) difference in overall survival between wide and narrow excision margins cannot be confidently ruled out.

The summary estimate for recurrence free survival favoured wide excision [Hazard Ratio 1.13; P = 0.06; 95% confidence interval 0.99 to 1.28] but again the result did not reach statistical significance (P < 0.05 level).

Current randomised trial evidence is insufficient to address optimal excision margins for primary cutaneous melanoma.

PLAIN LANGUAGE SUMMARY

Surgical excision margins for primary cutaneous melanoma

Whilst melanoma accounts for only 5% of skin cancers, it is important because it is the cause of 75% of all skin cancer deaths. For primary cutaneous melanoma, standard treatment is complete surgical removal of the melanoma with a safety margin some distance from the visible edges of the primary tumour. The purpose of the safety margin is to remove both the primary tumour and any melanoma cells that might have spread into the surrounding skin. However, the optimal width of the safety (excision) margin remains unclear.

This systematic review summarises the evidence about how much tissue (safety margin) should be removed for primary cutaneous melanoma (skin cancer). Excision margins are important because there could be a trade-off between a better cosmetic result but poorer long-term survival if excision margins become too narrow.

It is important to note that for the purposes of this review we consider only invasive melanoma - that has invaded into the deeper layer of the skin (dermis) - and not melanoma-in-situ where the melanoma cells are confined to the outermost layer of the skin (epidermis).

We found five published randomised trials, none of which showed a statistically significant difference in overall survival for patients who had either narrow or wide removal of the melanoma and surrounding tissue. Similarly, our meta-analysis showed there was no statistically significant difference in overall survival between the two groups treated with either narrow or wide excision.

The summary estimate for overall survival favoured wide excision by a small degree, but the result was not significantly different. This result is compatible with both a 5% relative reduction in overall mortality favouring narrower excision and a 15% relative reduction in overall mortality favouring wider excision.

Current randomised trial evidence is insufficient to address optimal excision margins for primary cutaneous melanoma.

BACKGROUND

Description of the condition

Melanoma or cutaneous melanoma, is a malignant neoplasm (cancer) arising from uncontrolled growth of melanocytes, the pigment-producing cells of the skin. It is a significant public health problem because it accounts for only 5% of total skin cancers but 75% of skin cancer deaths (Boring 1994). Furthermore, melanoma causes disproportionate mortality in people of young and middle age, such that an average of almost 20 years of potential life are lost

for each melanoma death in the US, one of the highest rates for adult-onset cancers (Cancer Statistics Review; Thompson 2005)
The incidence of melanoma is increasing annually (Thompson 2005). Approximately 2% (1 in 55) of people born in the US today are expected to develop melanoma (National Cancer Institute) compared to 1 in 1500 in the 1930s (Rigel 2000). Survival due to melanoma has been improving mainly due to earlier detection (Thompson 2005), and currently ranges from 67% for black men to 93% for white women in the US (National Cancer Institute). The World Health Organization (WHO) estimated that in 2000 the world incidence of melanoma was 132,602 with 37,047 deaths (28%). The US estimate for 2008, is that 62,480 people will be diagnosed with cutaneous melanoma with 8,420 deaths (13%) (National Cancer Institute).
Melanoma can develop either in a pre-existing pigmented lesion or de novo (from new) in previously normal looking skin. Features raising suspicion of melanoma in a pre-existing pigmented lesion include: change in size, irregular shape, irregular colour, diameter 7 mm or more, inflammation, oozing, and change in sensation (MacKie 1989; MacKie 1990). The ABCD system of diagnosis (Asymmetry, Border irregularity, Colour variegation, and a Diameter greater than 6 mm) has also been advocated to assist early clinical diagnosis (Friedman 1985), to which 'E' (Evolving or Elevation) has been added (Abbasi 2004). Epiluminescence microscopy (microscopic examination of the skin surface; dermoscopy) is sometimes used to improve diagnostic accuracy of pigmented lesions (Argenziano 2003). Suspicious lesions which have been biopsied should be excised completely and sent for confirmatory histopathological examination (ANZ Guidelines 2008). In situations where complete removal is not practical (for example, large site, difficult location), an initial incisional biopsy of the lesion should be considered. However, biopsy that does not assess the full thickness of the lesion (for example, superficial shave biopsy) should be avoided because histological thickness of invasion is the basic criterion for staging (Ng 2003).
Once melanoma is diagnosed clinically, the stage of the tumour is determined by pathological assessment. Tumour staging is important for treatment. The American Joint Committee on Cancer (AJCC) staging system (Balch 2009a) is recommended for general use in melanoma staging. In the AJCC system stage 0 (in-situ melanoma), stage I, and stage II are defined as localised melanoma, that is, the melanoma is localised to the skin and there is no regional or distant metastatic disease. Stage III melanoma occurs when there is regional metastasis (Balch 2009a). Stage IV melanoma occurs when there is distant metastasis (Balch 2009a). Eighty one percent of cases of cutaneous melanoma are diagnosed while the cancer is still confined to the primary site (localised stage); 12% are diagnosed after the cancer has spread to regional lymph nodes or directly beyond the primary site; 4% are diagnosed after the cancer has already metastasised to distant sites (distant stage), and for the remaining 4% the staging information was unknown. The corresponding 5-year relative survival rates were: 98.7% for localised; 65.1% for regional; 15.5% for distant; and 77.4% for unstaged (National Cancer Institute).
In this review, we are concerned only with primary cutaneous melanoma (Stage I and II melanoma (Balch 2009a)) which is confined to the skin and in which there is no clinical or histological evidence of metastatic disease. We will not consider or include melanoma that has spread or metastasised. In-situ melanoma (Stage 0), including lentigo maligna, is a distinct topic which will not be considered within this review. In in-situ melanoma, the malignant cells are solely confined to the epidermis and there is no invasion.
The Breslow thickness of a cutaneous melanoma is defined as the distance of invasion, as measured from the granular layer of the epidermis to the point of deepest invasion by the tumour cells (basically the depth or thickness of the melanoma, usually reported in millimetres). This is the most important prognostic indicator of localised disease (Balch 2003; Balch 2004). Once metastasis has been shown to have occurred, then this (metastasis) becomes the most important prognostic indicator (Balch 2003; Balch 2004). A thin melanoma with positive nodes has a worse prognosis than a thicker melanoma without them.
The average Breslow thickness of melanoma at the time of diagnosis has been decreasing in recent decades (Dennis 1999; Garbe 2001). This may be related to screening, and earlier presentation and detection of melanoma (Osborne 2002). Melanoma mortality has been increasing less rapidly than melanoma incidence, and localised melanoma accounts for an increasing proportion of incident cases.
The development of melanoma is associated with sun exposure, including intense intermittent solar exposure during childhood (Breitbart 1997; Naldi 2000). Melanoma risk has been shown to vary inversely with skin pigmentation, with the incidence rate in African Americans only one sixth of the rate found in the white-skinned population (Garrison 1996). A strong genetic predisposition for developing melanoma has also been observed for some individuals with dysplastic naevus syndrome (atypical mole syndrome) or a family history of melanoma (Thompson 2005; Newton-Bishop 2007).

Description of the intervention

Surgery is the only potentially curative treatment for primary cutaneous melanoma. Standard treatment is surgical excision with a safety margin, with all excised tissue being examined histologically. The purpose of the safety margin is to remove both the primary tumour and any melanoma cells that might have spread from the primary melanoma into the surrounding skin. If the cells have spread no further, and are all included in the safety margin, the operation would be curative.
Current recommendations for melanoma excision margins are based on the maximum Breslow thickness of the primary melanoma (as determined by the initial excision biopsy). In gen-

eral, wider excision is favoured for tumours with a less favourable prognosis, such as increased Breslow thickness. However, the extent of surgical excision margins that should be used for a given thickness of melanoma and the magnitude of benefit of different margins is unclear.

The depth of excision in usual clinical practice is excision down to but not including the deep fascia (ANZ Guidelines 2008). However, In facial areas where 'deep fascia' is less clearly defined (for example, on the ear, nose, or eyelid), or other anatomic sites such as over the breast, existing studies provide no clear guidelines for optimal depth.

Following the diagnosis of primary cutaneous melanoma (stage I, II) routine investigations are not required for asymptomatic individuals (ANZ Guidelines 2008). Although sentinel node biopsy is an important prognostic tool for melanoma (Morton 2006), there is debate about its therapeutic efficacy (Balch 2006; Gonzalez 2007; ANZ Guidelines 2008; Balch 2009).

From the individual's point of view, when faced with a diagnosis of melanoma, the most important consideration is to make sure that it is removed with as much certainty as possible that it is all gone! The size and depth of the excision should therefore err on the side of safety first. However, quality of life after surgery is an important consideration and unnecessary disfigurement should be avoided.

Why it is important to do this review

On the basis of the erroneous interpretation of a single histology specimen, Handley first suggested the removal of 2 inches (5 cm) of subcutaneous tissue down to the level of muscle fascia, together with the radical removal of lymph nodes (Handley 1907). This set the 'rules' for surgical management of primary cutaneous melanoma for many years (Eedy 2003). However, in 1977 Breslow and Macht questioned the need for wide excision when they reported no adverse events in a small series of people with melanomas $\leq$ 0.75 mm who underwent narrow excision (Breslow 1977). Since then, the margins for excising primary cutaneous melanoma have been reduced considerably since Handley's initial report of a case of metastatic melanoma in 1907 (ANZ Guidelines 2008).

Current national guidelines for excision margins for primary cutaneous melanoma for the UK (Roberts 2002; Newton-Bishop 2007), US (National Comprehensive Cancer Network), Australia (ANZ Guidelines 2008), Switzerland (Dummer 2005), The Netherlands (van Everdingen 2005), Germany (Garbe 2008) are shown in Table 1 (Current national guidelines for excision margins for primary cutaneous melanoma). Although these various guidelines provide some consistent generalisations regarding the width of excision margins, they do offer slightly different advice. Each guideline is based on the 'best' interpretation of the available evidence at the time of guideline publication. Presumably, the variation in published recommendations relates to difficulty in data interpretation.

Table 1. Current national guidelines for excision margins for primary cutaneous

Breslow Thickness	UK (2002)	US (2009)*	Australian (2008)	Swiss (2005)	Dutch (2005)	German (2008)
In-situ	2 to 5 mm	5 mm	5 mm	5 mm	5 mm	5 mm
$\leq$ 1 mm thick	1 cm	1 cm	1 cm	1 cm	1 cm	1 cm
1.01 to 2 mm thick	1 to 2 cm	1 to 2 cm	1 to 2 cm	1 cm	1 cm	1 cm
2.01 to 4 mm thick	2 to 3 cm	2 cm	1 to 2 cm**	2 cm	2 cm	2 cm
> 4 mm thick	2 to 3 cm	2 cm	2 cm	2 cm	2 cm	2 cm

* 'Margins may be modified to accommodate individual anatomic or functional considerations.'

** 'Caution be exercised for melanomas 2 to 4 mm thick, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2 cm) for these tumours depending on tumour site and surgeon/patient preference.'

A few randomised trials have examined the impact of melanoma excision margins on mortality. However, these trials individually have limited power and follow-up. Most of these trials excluded melanoma on the face, and generally did not study melanoma of the digits or subungual (beneath fingernails or toenails) melanomas. It is unclear whether data on truncal lesions can be extrapolated, for example, to facial lesions.

Three systematic reviews and meta-analyses examining excision margins for primary cutaneous melanomas have previously been published (Lens 2002; Haigh 2003; Lens 2007). However, optimum margin size remains unclear.

Wider excision margins may result in additional hospital inpatient stay, more costly procedures such as skin grafting, increased anaesthetic requirements and increased cosmetic disfigurement and can be associated with wound complications and lymphoedema (Cassileth 1983; O'Rourke 1993). Narrower excision margins may result in higher local recurrence rates or higher mortality, or both (Dong 2000; Ng 2001). Either too narrow or too wide margins may adversely affect quality of life (QOL) or physical or psychological morbidity, contribute to other adverse events, and increase cost to society via either over treatment or recurrence from under treatment. The impact of these risks on individuals and society and the apparently wide range of excision margins in practice compel systematic review.

We performed this Cochrane review to assess the effects of different excision margins for primary cutaneous melanoma.

OBJECTIVES

To assess the effects of different widths of excision margins on primary cutaneous melanoma. For the purposes of this review we excluded melanoma in-situ.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

We included all participants (all ages, all ethnic groups) with primary cutaneous melanoma confirmed histologically on biopsy, without metastases (AJCC/UICC [International Union Against Cancer] Stage I and II). We included all Breslow thicknesses.
Individuals diagnosed with in-situ melanoma (Stage 0) are not considered within this review.

Types of interventions

We included all randomised trials of surgical excision of primary cutaneous melanoma which compared different widths of excision margins. We did not pre-define narrow and wide margins (in terms of centimetres) because of the considerable variation in definition of margin width among included trials.
We excluded studies not including Breslow thickness or other pertinent/prognostic data.
In all of the trials, investigators measured excision margins clinically (they were not histologically determined margins).

Types of outcome measures

Primary outcomes

1. Time to death (any cause)
2. Time to combined endpoint of death (any cause) or recurrence (local, in transit, regional, distant).
Recurrence is considered as an outcome only as a 'combined endpoint of death or recurrence' because analysis of recurrence alone can be misleading; this is because, death in the absence of recurrence is counted along with survival in the absence of recurrence, as a good outcome (Lubsen 2002). Furthermore, caution is needed when interpreting local recurrence data because reduced local recurrence may not translate to survival benefit.

Secondary outcomes

1. Quality of Life

a) Global, e.g. Psychological Adjustment to Illness Scale (PAIS) (Derogatis 1986)
b) Physical, e.g. scar questionnaire (Cassileth 1983)
c) Social, e.g. Medical Outcomes Study (MOS)36 (Ware 1992)
d) Psychological, e.g. Hamilton Anxiety and Depression (HAD) score (Skarstein 2000)
We stated the broad areas in which quality of life can be measured, together with specific measures as examples for each group. The precise measures used in our final analysis were determined by those measures used in individual studies.

2. Adverse events/outcomes

a) Surgical, e.g. severe surgical complications, grafting versus primary closure
b) Non-surgical, e.g. length of hospital inpatient stay, local versus general anaesthetic, adverse drug reactions (e.g. to antibiotics, analgesics, anaesthetics)

Search methods for identification of studies

Electronic searches

We searched for relevant trials from:

- The Cochrane Skin Group Specialised Register on 3rd August 2009 using the terms melan* and excis*;
- The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 3, 2009) using the search strategy in Appendix 1;
- MEDLINE (from 2005 to 3rd August 2009) using the search strategy in Appendix 2;
- EMBASE (from 2007 to 3rd August 2009) using the search strategy in Appendix 3;

The UK Cochrane Centre (UKCC) has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2004 and in EMBASE to 2006. Further searching has been undertaken for this review by the Cochrane Skin Group to cover the years that have not been searched by the UKCC.

- CINAHL (from 1982 to 2004) using the search strategy in Appendix 4;
- AMED (Allied and Complementary Medicine, from 1985 to 2004) using the search strategy in Appendix 5;
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the search strategy in Appendix 6; and
- Science citation index using the search strategy in Appendix 7.

Ongoing Trials Databases

We searched the following ongoing trial databases on 3rd August 2009, using the terms 'melanoma' and 'excision':

- The metaRegister of Controlled Trials www.controlled-trials.com;
- The U.S. National Institutes of Health ongoing trials register www.clinicaltrials.gov;
- The Australian and New Zealand Clinical Trials Registry www.anzctr.org.au;
- The World Health Organization International Clinical Trials Registry platform www.who.int/trialsearch; and
- The Ongoing Skin Trials register on www.nottingham.ac.uk/ongoingskintrials.

Searching other resources

References from published studies

We checked all references from published trials for references to other studies.

Unpublished literature

We wrote (by airmail and email) to the corresponding authors of all (five) located RCTs asking for information about unpublished trials, on-going trials and grey literature. We received responses from all apart from the WHO trial authors. Trialists were not aware of any further other non-published RCTs.

Adverse events

We performed a search for side-effects, limited to studies which compare different excision margins. Non-randomised studies were considered using the search strategy in Appendix 8.

Other

Our search terms were in English except for the search of LILACS. Apart from this, no language restrictions were imposed.

Data collection and analysis

Selection of studies

Two authors performed independent searches for trials (MS, AF). We (MS, AF) then checked the titles and abstracts identified from the searches and obtained the full text of all studies of possible relevance. These two authors independently decided which trials fitted the inclusion criteria and recorded the methodological quality. There was no disagreement between the authors about these aspects of study selection. There were no excluded studies.

Data extraction and management

Two authors (MS, AF) extracted data and independently entered data onto a customised data extraction form (based on the template obtained from the Cochrane Skin Group). There were no discrepancies between the two authors. One author (SH) then checked and entered the data into RevMan. One author (SH) carried out the analysis. Authors were not blinded to the names of authors, journal, or institutions.

Assessment of risk of bias in included studies

We assessed methodological quality, particularly addressing the following areas, since these may be associated with biased estimates of treatment effect (Higgins 2008):
(a) the method of generation of the randomisation sequence;
(b) the method of allocation concealment - it was considered 'adequate' if the assignment cannot be foreseen;
(c) who was blinded/not blinded (participants, clinicians, outcome assessors) - blinding was not deemed to be of great importance in interpreting the primary outcomes (death and recurrence). For

secondary outcomes, we considered blinding of the outcome assessor most important; and
(d) how many participants were lost to follow-up in each arm (split into postrandomisation exclusions and later losses if possible), and whether participants were analysed in the groups to which they were originally randomised.
We recorded the information in the 'Risk of bias' tables which are part of the 'Characteristics of included studies' table.

Measures of treatment effect

We used hazard ratios (HR) for the primary analysis which summarise the average effect over the duration of follow-up. Actuarial rates were summarised by duration of follow-up, at medium-term (5 year) and long-term (10 year) time points (Table 2, actuarial rates of overall survival and recurrence-free survival at 5 and 10 years).

Table 2. Actuarial rates of overall survival and recurrence free survival at 5 and 10 yrs

		NARROW EXCISION	WIDE EXCISION
Overall survival			
5 year	French	93%	90%
	Intergroup	76%	82%
	Swedish	86%	89%
	WHO (4 year)	97%	96%
	BAPS/MSG	NR	NR
10 year	French	87%	86%
	Intergroup	70%	77%
	Swedish	79% (75%, 82%)	76% (72%, 80%)
	WHO (8 year)	90%	90%
	WHO (12 year)	87%	87%
	BAPS/MSG	NR	NR

Table 2. Actuarial rates of overall survival and recurrence free survival at 5 and 10 yrs (*Continued*)

Recurrence-free survival			
5 year	French	NR	NR
	Intergroup	75%	80%
	Swedish	81% (77%, 84%)	83% (80%, 86%)
	WHO (4 year)	NR	NR
	BAPS/MSG	NR	NR
10 year	French	85%	83%
	Intergroup	NR	NR
	Swedish	71% (66%, 75%)	70% (65%, 74%)
	WHO (8 year)	82%	84%
	BAPS/MSG	NR	NR

NR = not reported
WHO = World Health Organisation
BAPS/MSG = British Association of Plastic Surgeons, Melanoma Study Group

We extracted all available summary statistics from all reports of the included trials for the outcome measures specified in the protocol. We directly estimated hazard ratios from coefficients of Cox proportional hazards model where available, including those with adjustment for prognostic factors. We then estimated the hazard ratio and the standard error of the log hazard ratio using the following methods (based on those reported by Parmar et al), (Parmar 1998; Williamson 2002) listed in order of preference:

1. HR reported with confidence interval or log-rank P value. Standard error estimated from confidence interval or P value (confidence interval used if both available). This is the preferred method since the hazard ratio is directly extracted and the standard error is estimated very accurately.

2. Adjusted HR reported with confidence interval or Cox Proportional Hazards P value. Standard error estimated from confidence interval or P value (confidence interval used if both available). This will on average give an estimate close to the unadjusted HR, but different studies adjust for different factors, and the choice of adjustment factors could be data-driven leading to bias.

3. Numbers of events reported with log-rank P value. HR estimated from numbers of events, standard error estimated from this estimated HR and P value. This gives a direct estimate of the HR since all events are considered, but may not be close to the actual HR particularly if the hazards are not proportional.

4. Actuarial rates at fixed follow-up and log-rank P value. This gives an estimate of the HR similar to that of method three, but only events up to the fixed follow-up time are considered.

Where several papers were available reporting different summary statistics for a trial, the primary consideration in selecting results to be entered into the meta-analysis was the type of summary data available, in order of preference as described above. We preferred data with longer follow-up.

We combined the estimated HRs using the generalised inverse method, on a logarithmic scale using meta-analysis methods and present the results as pooled hazard ratios with 95% confidence intervals (CI).

Dealing with missing data

We did not contact the study authors concerning the small amount of missing data and slight variation in reported study numbers.

Assessment of heterogeneity

We assessed statistical heterogeneity using I^2 statistic, as well as visually from the analysis.
Before starting this Cochrane review, we already knew that there would be a degree of clinical diversity (heterogeneity) between studies, for example, that different widths of excision are used in different studies. We discuss these issues as limitations to our review.

Data synthesis

We used a fixed-effect model of meta-analysis for data synthesis.

Subgroup analysis and investigation of heterogeneity

If possible, we planned to perform subgroup analysis based on (i) melanoma thickness and (ii) body site of melanoma.
To enable this process, we wrote to all study authors requesting further primary data. At the time of writing of this report, we had obtained further data only from the Intergroup and Swedish trials (Analysis 2.1). The authors of the French trial and the BAPS/MSG trial were unable to provide further data. At the time of writing of this report, we had received no reply from the WHO study group.
There were insufficient data to perform a subgroup analysis based on Breslow thickness of melanoma.
There were insufficient data to perform a subgroup analysis based on body site of melanoma.

Sensitivity analysis

We explored the potential impact of different methods of estimation by comparing results estimated using different methods where suitable summary data were available. We also performed a sensitivity analysis excluding results extracted using the methods considered less reliable.

Consumer involvement

A consumer (TH) was consulted throughout, particularly for readability and understanding of the final review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of ongoing studies.
We identified five RCTs of surgical excision of primary cutaneous melanoma which compared different width excision margins. These included a total of 1633 participants in the narrow excision margin group, and 1664 in the wide excision margin group, making a total of 3297 participants. The five RCTs were published in 11 separate reports. The RCTs were: BAPS/MSG study (British Association of Plastic Surgeons, Melanoma Study Group) (Thomas 2004), French study (Khayat 2003), Intergoup study (Balch 2001), Swedish study (Cohn-Cedermark 2000), and the WHO study (Cascinelli 1998).
We found no additional studies (comparing different excision margins) which further assessed adverse event or quality of life outcomes.

Results of the search

We identified 5 randomised trials, published in 11 reports (1988 to 2004). We have listed, in brief, the characteristics of each study below and describe these in detail in the tableof 'Characteristics of included studies'. All trials were multicentre, and four were multinational.
Our initial search strategies located approximately 800 titles, but none of the remaining titles pertained to randomised trials.
The studies differed in eligibility criteria and were clinically heterogeneous in nature, as described below (and listed fully in the ' Characteristics of included studies'). They considered melanomas of different thickness, different tumour sites, and used different widths of excision margin. In all the trials, the participating dermatologist/surgeon measured excision margins clinically. There are no data given in the studies correlating clinical margins with histological margins. In all the trials, pathologists confirmed the diagnosis of melanomas histologically. The definitions of recurrence varied between studies; however, these definitions were not always clearly and precisely stated in the trials. Management of regional nodes also varied between trials.
The results of the Swedish Melanoma Study Group study comparing 2 cm excision margins with 4 cm excision margins for melanomas thicker than 2.0 mm are still awaited (Ringborg 2005).
We could not identify any other unpublished studies which were eligible for inclusion in the review.

Included studies

The five included trials compared different excision margins as follows:

- Two RCTs (BAPS and WHO) compared 1 to 3 cm excision margins
- One RCT (Intergroup) compared 2 to 4 cm excision margins
- Two RCTs (French and Swedish) compared 2 to 5 cm excision margins

BAPS/MSG Study

One published report of this trial (Thomas 2004).
Single, primary, localised cutaneous melanoma 2 mm or greater in thickness.
Local excision with either a 1 or 3 cm margin.
Nine hundred participants were randomised, 453 to the 1 cm excision group and 447 to the 3 cm excision group.
Local recurrence was defined as a recurrence within 2 cm of the scar or graft. In-transit recurrence was defined as a recurrence from beyond the first 2 cm of the scar or graft to the regional nodes. All locoregional recurrences were detected clinically and confirmed by biopsy. Of note, the primary endpoint of local recurrence was changed part way through the trial, so that these end points were combined in the final analysis.
Sentinal lymph node biopsy was not routinely performed. The paper suggests that nodal surgery was undertaken only if disease became clinically apparent during follow-up.

French Study

Two published reports of this trial can be found under (Khayat 2003).
Maximum tumour thickness was 2 mm, stage 1 disease as defined by Tumour Node Metastases (TNM) criteria.
Local excision with either a 2 or 5 cm margin.
Three hundred and thirty-seven participants were randomised, 167 to the 2 cm group and 170 to the 5 cm group.
Local disease recurrence was defined as recurrence within 2 cm of the scar. In-transit metastases was defined as disease recurrence between the primary tumour site and the regional lymph node.
Sentinal lymph node biopsy was not performed. Regional tumours that recurred were removed surgically.

Intergroup Study

Three published reports of this trial can be found under (Balch 2001).
Cutaneous melanoma of thickness 1.0 to 4.0 mm and no evidence of metastatic melanoma in regional lymph nodes or at distant sites.
Local excision with either a 2 or 4 cm margin.
Four hundred and eighty-six participants were randomised (244 = 2 cm, 242 = 4 cm) (1993 report) (1996 paper states 470; 2001 paper states 468).
Local recurrence was defined as a biopsy-proven first recurrence within 2 cm of the scar. 'If a patient with multiple in-transit (intralymphatic) metastases had a lesion within 2cm of the scar, it was not counted as a local recurrence. Once the patient had distant metastases, synchronous tumour recurrences in and around the surgical scar were not counted as a local recurrence because they were more likely a manifestation of distant metastasis.'
'Each participant was also randomly assigned to receive ELND (elective lymph node dissection) or observation of the regional lymph nodes with delayed lymph node dissection only if clinically indicated.' 'participants receiving ELND were evenly distributed between the two treatment arms involving surgical margins, so any survival differences that may result from ELND would not influence the survival outcome from the surgical margin issue.'

Swedish Study

Two published report of this trial can be found under (Cohn-Cedermark 2000).
Cutaneous melanoma measuring > 0.8 mm and $\leqq$ 2.0 mm in thickness.
Local excision with either a 2 or 5 cm margin.
Nine hundred and eighty-nine participants were randomised, 476 to the 2 cm excision group, 513 to the 5 cm excision group.
Local recurrence was defined as a recurrence in the 'scar or transplant'. Other forms of recurrence are not defined.
Sentinal lymph node biopsy was not routinely performed. The paper suggests that nodal surgery was undertaken only if disease became clinically apparent during follow-up.

WHO Study

Three published reports of this trial can be found under (Cascinelli 1998).
Cutaneous melanoma 2 mm or less in thickness.
Local excision with either a 1 or 3 cm margin. Of note, 'the excisions had to be 1 or 2 cm wider in the subcutaneous fat extending to the muscular fascia', so the true width of excision might be unclear.
Seven hundred and three participants were randomised, of which 612 (87%) were evaluated.
The 1988 paper states that 'local recurrences and in-transit and nodal metastases *were* defined as in the TNM staging system (IUAC, 1978)'. The 1991 paper states that local recurrence was defined as cutaneous or subcutaneous nodules in scar or within 1cm of scar.
Regional lymph nodes were not scheduled for removal.

Excluded studies

We did not exclude any RCTs of surgical excision of melanoma which compared different width excision margins.

Risk of bias in included studies

Randomisation

The Intergroup trial design utilised the method of Zelen randomisation, a reasonable and accepted approach of the 'day', but one which has since proved controversial.

Zelen (Zelen 1979) proposed this novel 'randomised consent' design, whereby participants are asked for their consent after rather than before randomisation, with the aim of increasing recruitment by avoiding some of the problems associated with obtaining informed consent. Altman (16 years later) discusses the reasons for and against the use of this study design and concludes that 'there are serious statistical arguments against the use of randomised consent designs, which should discourage their use' (Altman 1995).

Some of the trials used stratification to achieve balance. In the BAPS/MSG study, stratification was performed by centre and the extent of primary surgery. Permuted blocks of random size were used. In the Swedish Melanoma Study Group trial, the random allocation was done using balanced lists. At three of the trial centres, separate lists for each participating hospital were used. At the remaining two centres, there was no stratification by hospital.

No specific details of how the random scheme was generated were reported for any of the trials.

Allocation

Two of the studies, the BAPS/MSG and Swedish trials, had sufficient description of the study methods to indicate that adequate concealment of allocation had occurred. The BAPS/MSG trial achieved allocation concealment using centralised telephone randomisation. The Swedish trial used randomisation lists, but the personal data of each randomised participant and the tumour thickness were noted on the list before the assigned treatment was revealed.

In the WHO study, the co-ordinating centre sent each participating centre a series of sealed envelopes, each containing a randomisation number and the treatment to be assigned. A copy of the randomisation series was kept by a secretariat so the randomisation procedure of each centre could be checked. There was no mention of the opaqueness of the envelopes. The Cochrane handbook (Higgins 2008) implies that sealed envelopes constitute unclear allocation concealment unless they are also described as sequentially numbered and opaque, so we have classed the WHO trial as unclear allocation concealment.

In the other two studies, there was no mention of any allocation concealment.

Blinding

Due to the nature of the intervention it is not possible to blind either participants or treating clinicians in these trials. However, detection bias is likely to be reduced if the outcome assessors are blinded. For overall survival, substantial detection bias is unlikely even with no blinding.

In the Intergroup trial, the principal investigator reviewed all deaths and was blinded as to the surgical treatment involved. However, this will primarily provide protection against detection bias in disease-specific mortality, which is not an outcome considered in this review.

In the BAPS/MSG study, French study, the Swedish Melanoma Study Group trial, and the WHO study reports, blinding of outcome assessors was not clear.

Incomplete outcome data

Handling of losses and attrition bias

- The BAPS/MSG study was reported as intention-to-treat (ITT), but no details were given.
- The French study analysis was not ITT as 337 patients were enrolled (presumably randomised) and only 326 evaluable patients were reported. Exclusions were due to not meeting eligibility criteria (n = 11).
- The Intergroup study does not state whether the study was ITT analysis; however, it would seem that ineligible patients were excluded from analysis.
- The Swedish study is reported as ITT, but no details were given.
- In the WHO study, the analysis was not ITT as 703 patients were randomised and only 612 evaluable patients were reported. Exclusions were due to not meeting eligibility criteria (n = 59), patients with head and/or neck tumours allocated to wide excision but not having a margin of at least 3cm (n = 16), "mistake in treatment" (n = 15), or lost to follow-up (n = 1).

Follow-up

As indicated in the table of 'Characteristics of included studies', not all the trials were intention-to-treat, and all trials had lost or missing data, or incomplete follow-up.

In the BAPS/MSG study, 900 participants were initially randomised. However, 10 participants (1.1%) were lost to follow up immediately after randomisation. Although the authors state that 'all analyses were conducted according to intention-to-treat ' it is not clear whether or not these ten participants are actually included in analyses.

In the French study (2003), of 337 participants initially randomised 11 were ineligible, leaving 326 evaluable participants (97%). The authors state that, after nearly 20 years of follow-up,

286 participants were evaluable for survival. It appears that the study was not fully analysed according to the intention-to-treat principle.
The most recent Intergroup trial publication (2001 report) reported survival in 468 randomised participants (238 with a 2 cm margin and 230 with a 4 cm margin), which is 96% of the original 486 participants. The Intergroup publication from 1996, however, reports results from 470 participants (238 with a 2 cm margin and 232 with a 4 cm margin), which is 97% of the original number of participants who were randomised. The 3 to 4% of patients not reported were those judged to be ineligible or not evaluable (Dr Charles Balch, personal communication).
In the Swedish Melanoma Study Group trial (2000 report), only 5 participants (0.5%) were lost to follow-up.
In the WHO study, 703 participants were initially randomised (1988 report) of which 612 (87%) were finally evaluated (1998 report); however, the authors do not comment about loss to follow-up in any of their 3 reports.
We did not contact the study authors concerning the small amount of missing data and slight variation in reported study numbers.

Selective reporting

The amount of missing data was small and unlikely to affect the conclusions.

Other potential sources of bias

As indicated, not all the trials were intention-to-treat, and all trials had lost or missing data, or incomplete follow-up.
In two of the trials, the Intergroup study and the French study, patients were further randomised to receive further treatment (elective lymph node dissection and Isoprinosine, respectively). It is not clear how this might influence the overall results.

Effects of interventions

Overall, the 5 identified randomised trials included a total of 1633 participants in the narrow excision margin group, and 1664 in the wide excision margin group. Narrow margin definition in these studies ranged from 1 to 2 cm, whereas wide margins ranged from 3 to 5 cm. Median follow-up for these studies ranged from 5 to 16 years.

Primary Outcomes

1. Time to death (any cause)
2. Time to combined endpoint of death (any cause) or recurrence (local, in transit, regional, distant)

All five studies reported data on survival and recurrence. However, exact definitions of recurrence varied from trial to trial, as described in the above section Description of studies and in the 'Characteristics of included studies' table.

The results for overall survival are shown in Analysis 1.1. The point estimate for overall survival favoured wide excision by a small degree [Hazard Ratio 1.04, 95% confidence interval 0.95 to 1.15], but the result did not reach statistical significance at the $P < 0.05$ level. This result is compatible with both a 5% relative reduction in overall mortality favouring narrower excision and a 15% relative reduction in overall mortality favouring wider excision.
The point estimate for recurrence-free survival based on the BAPS/MSG and Swedish trials (Analysis 1.2) favoured wide excision [Hazard Ratio 1.13, $P = 0.06$, 95% confidence interval 0.99 to 1.28] but the result did not reach statistical significance at the $P < 0.05$ level. This result is compatible with both a 1% relative reduction in mortality favouring narrower excision and a 15% relative reduction in mortality favouring wider excision.
No substantial heterogeneity was observed for either of the two primary outcome measures.
Medium (approximately 5 year) and long-term (approximately 10 year) outcomes (overall survival and recurrence-free survival) are tabulated in Table 2 (actuarial rates of overall survival and recurrence free survival at 5 and 10 years). There was insufficient detail reported in the trials to allow more formal analysis or meta-analysis, for example, the number of participants still at risk.
The five trials used number of events, hazard ratio, and actuarial rates to report their outcomes. We performed a sensitivity analysis excluding results extracted using actuarial rates rather than hazard ratios, which showed little impact on the results. Figure 1 and Figure 2 show the consistency of the estimated hazard ratio and confidence interval based on the various extraction methods for overall survival and recurrence-free survival respectively. Overall there were some differences in the estimated results according to the method of estimation, but there was considerable overlap of confidence intervals.

Figure 1. Sensitivity analysis: Variation in estimated hazard ratio and 95% CI for overall survival based on method of reporting outcome data (hazard ratio, number of events, and actuarial rates)

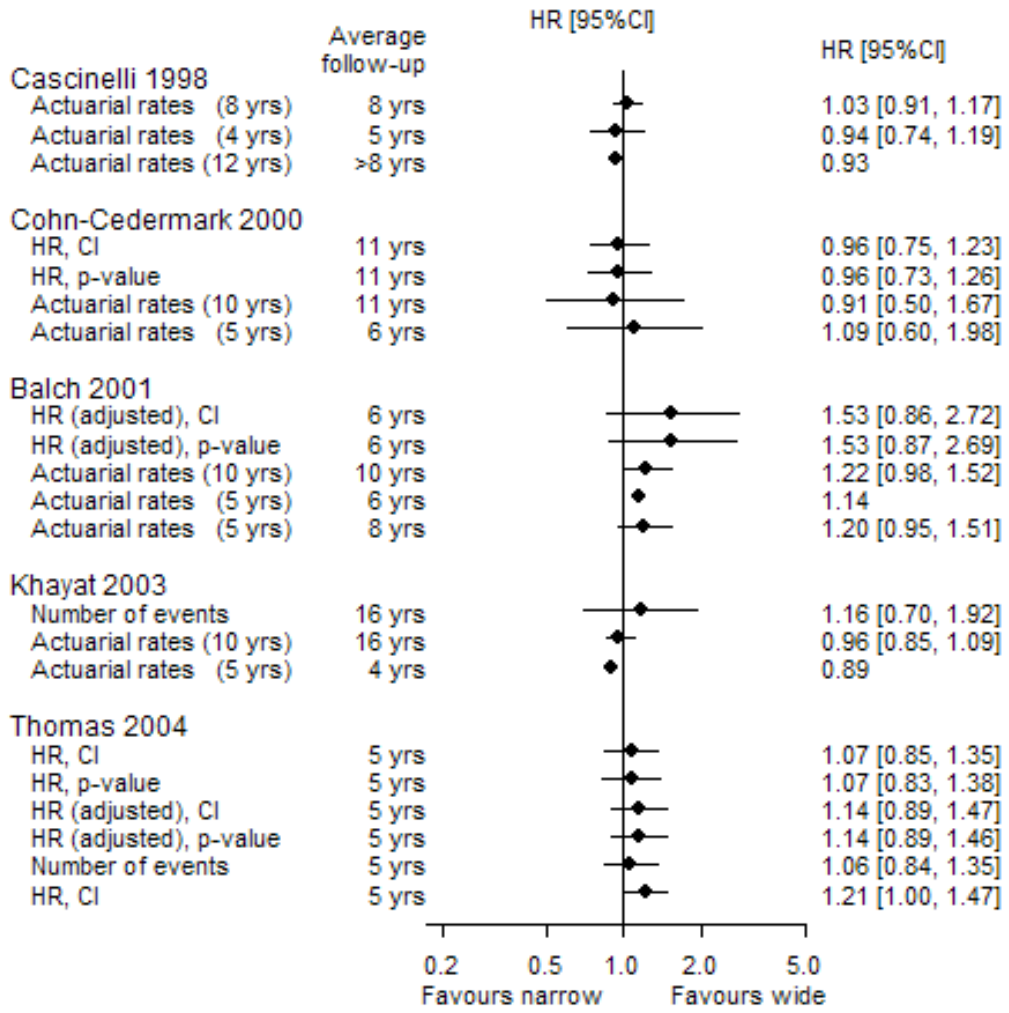
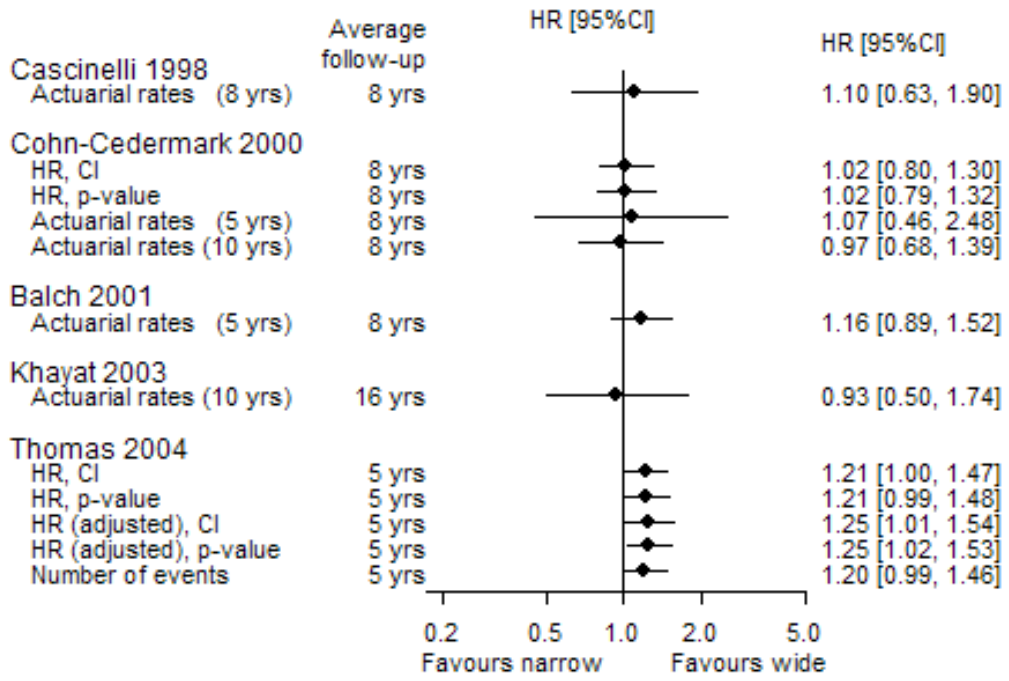


Figure 2. Sensitivity analysis: Variation in estimated hazard ratio and 95% CI for recurrence-free survival based on method of reporting outcome data (hazard ratio, number of events, and actuarial rates)



Secondary outcomes

1. Quality of Life

a) Global, e.g. Psychological Adjustment to Illness Scale (PAIS) (Derogatis 1986)
b) Physical, e.g. scar questionnaire (Cassileth 1983)
c) Social, e.g. Medical Outcomes Study (MOS) 36 (Ware 1992)
d) Psychological, e.g. Hamilton Anxiety and Depression (HAD) score (Skarstein 2000)

A quality of life study was carried out as part of the BAPS/MSG trial and reported in a separate publication [Newton-Bishop 2004]. Data were collected from 426 of 537 participants who were mailed the questionnaires, a response rate of 79%.

The study had 2 aims. First, to test the hypothesis that melanoma participants treated with a 3 cm excision margin suffer greater impairment of their quality of life than those treated with a 1 cm margin. Second, to determine the predictors of a poor participant perception of their excision scar. The questionnaire utilised the Hospital Anxiety and Depression (HAD), Psychosocial Adjustment of Illness Scale-Self-Report (PAIS-SR), Medical Outcomes Survey-Short Form 36 (MOS-SF36), and the Cassileth Scar questionnaires.

The results of the study showed that participants treated with a 3 cm excision margin had significantly poorer physical and mental function (as defined by physical component summary [PCS] and mental component summary [MCS] of the MOS-SF36) than the narrow margin group 1 month after surgery (P = 0.003 and 0.008, respectively). The magnitude of effect is shown graphically; all results appear to lie within the overall UK population mean plus/minus 1 standard deviation. However, from 6 months onwards, there was little difference in PCS and MCS scores (P = 0.85, P = 0.63) between the 2 groups.

Those treated by a 3 cm margin reported a poorer perception of their scar than those treated by a 1 cm margin, a difference which persisted throughout the study period. The overall magnitude of this difference was statistically significant (scar scores were 19% lower in the wide margin group; 95% CI 15% to 23%; P < 0.0001) but it is unclear how this related to people in clinically meaningful terms.

The authors concluded that the use of a 3 cm excision margin for melanoma is associated with significantly more morbidity than use of a 1 cm margin, but that this effect disappeared by 6 months. However, those participants treated by 3 cm excision were more likely to have a persistent poor view of their scar.

2. Adverse events/outcomes

a) Surgical - e.g. severe surgical complications, grafting versus primary closure
b) Non-surgical - e.g. length of hospital inpatient stay, local versus general anaesthetic, adverse drug reactions (for example, to antibiotics, analgesics, anaesthetics)
Only two trials, the Intergroup and the BAPS/MSG, reported adverse event outcome measures.
The Intergroup trial assessed: skin grafting, hospital stay, wound infection rate, wound dehiscence (skin separation) rates:

- The rate of skin grafts was reduced from 46% with 4 cm surgical margins to 11% with 2 cm surgical margins (P < 0.001).

- For the entire study cohort (this includes patients who underwent elective lymph node dissection as part of the protocol, as well as those who did not have ELND), the hospital stay was reduced from 7.0 days for participants receiving 4 cm surgical margins to 5.2 days for those receiving 2 cm margins (P = 0.0001). For those who did not have ELND, the hospital stay was reduced from 5.2 days for participants receiving 4 cm surgical margins to 3.0 days for those receiving 2 cm margins (P = 0.001). This reduction in length of hospital admission was mainly due to the reduced need for skin grafting, since the hospital stay for those who had a skin graft was 3.5 days longer than that for those who had a primary wound closure (6.5 days versus 3.0, P < 0.01).

- There was no significant difference between wound infection rates (4.6% and 5.4%) between the 2 groups (4 and 2 cm margins respectively).

- There was no significant difference between wound dehiscence rates (4.2% and 4.6%) between the 2 groups (4 and 2 cm margins respectively).

The BAPS/MSG trial stated that the rate of surgical complications was 7.8% among participants with a 1 cm excision margin compared with 13.9% among those with a 3 cm excision margin (P = 0.05).
For the WHO trial, it was stated that "the frequency of adverse events during follow-up was similar in the two groups when regional lymph node metastases, in-transit metastases, and metastatic spread to distant sites were taken into consideration".

Overall survival and Breslow thickness

There were insufficient data to perform a subgroup analysis of overall survival stratified by Breslow thickness. However, it is important to note the numbers of participants with melanomas of different Breslow thickness:

- **Melanomas < 1 mm thick**

Three RCTs included 762 (159 French, 244 Swedish, 359 WHO) participants with melanomas < 1 mm thick. Of these, only 185 (in the WHO study) were treated with a 1 cm excision margin. There is insufficient RCT data on which to base clinical recommendations, although a 1 cm margin is widely accepted as standard treatment for thin (<1mm) melanomas.

- **Melanomas 1 to 2 mm thick**

Four of the RCTs, the French, Swedish, WHO, and Intergroup trials, included participants who had melanomas between 1 and 2 mm thick. None of these trials demonstrated a statistically significant difference in overall survival between the two groups who were treated with narrow or wide excision.

- **Melanomas < 2 mm thick**

Three of the RCTs, the French, Swedish and WHO trials, assessed melanomas less than 2 mm thick, whilst 290 participants in the Intergroup study had melanomas between 1 mm and 2 mm thick. None of these trials demonstrated a statistically significant difference in overall survival between the two groups who were treated with narrow or wide excision.

- **Melanomas 2 to 4 mm thick**

Two RCTs included participants who had melanomas between 2 and 4 mm thick, the Intergroup trial (190 participants) and the BAPS/MSG trial (approximately 660 participants). In the larger BAPS/MSG trial, there was no statistically significant difference in overall survival between the 2 groups who were treated with narrow (1 cm) or wide (3 cm) excision.

- **Melanomas > 4mm thick**

Approximately 240 participants in the BAPS/MSG study had melanomas > 4mm thick. Most international guidelines suggest an excision margin of 2 to 3 cm for these tumours but there are limited data on which to base this advice.

DISCUSSION

Summary of main results

This systematic review summarises the evidence regarding the width of surgical excision margins for primary cutaneous

melanoma. None of the five published trials has shown a statistically significant difference in overall survival when comparing narrow with wide excision. Furthermore, our meta-analysis has not shown a statistically significant difference in overall survival between the two groups that were treated with narrow or wide excision.

The point estimate for overall survival favoured wide excision by a small degree [Hazard Ratio 1.04, 95% confidence interval 0.95 to 1.15, P = 0.40] but the result was not significantly different. This result is compatible with both a 5% relative reduction in overall mortality favouring narrower excision and a 15% relative reduction in overall mortality favouring wider excision. Therefore, a small (but potentially important) difference in overall survival between wide and narrow excision margins cannot be confidently ruled out, such as a 10 year survival rate of 85% compared to one of between 81% and 87%.

The point estimate for recurrence-free survival favoured wide excision [Hazard Ratio 1.13, P = 0.06, 95% confidence interval 0.99 to 1.28] but the result did not reach statistical significance at the $P < 0.05$ level. This result is compatible with both a 1% relative reduction in mortality favouring narrower excision and a 15% relative reduction in mortality favouring wider excision.

Overall completeness and applicability of evidence

Although we requested further primary data (numbers of death versus Breslow thickness) for all the trials, this information was available from only two of the trials, the Intergroup and the Swedish trials. This limited our ability to perform a detailed meta-analysis and consequently reduced our capacity to define the optimal widths of surgical excision margins for primary cutaneous melanoma. This problem was compounded by the heterogeneity of the excision margins used in individual trials. Further, there are limited RCT data assessing treatment of thin melanomas < 1 mm and thick melanomas $\geq$ 4 mm.

The five trials included in our review do not adequately address the issues of melanomas in specific body sites, such as head and neck, distal extremities, hands (including fingers and subungual melanomas), and feet.

In particular, the relative paucity of available RCT data leaves clinicians with little guidance on the clinical management of facial melanomas (only the French study included melanomas on the head and neck and this involved only 16 participants). There are differences between facial melanomas and those on the trunk or extremities and it is unclear whether data on truncal lesions can be extrapolated to facial lesions. For example, recommendations for depth of excision which are typically 'to fascia' are difficult to apply on the nose or eyelid or ear, because in these sites the fascia may be less well defined. The morbidity (particularly 'cost' for reconstruction or potential disfigurement) associated with wider excisions on the face is likely to be greater than for those on the trunk. For example, even 1 cm margins are potentially problematic in critical facial locations. For this reason, some experts have advocated narrower margins on the face but there are no RCT data to help determine the consequences on mortality or recurrence of these narrower margins.

Management of digital melanomas including the subset of subungual melanomas often includes partial amputation. As with facial lesions, there are no RCTs available to help determine if less aggressive surgery would be as effective.

The RCTs, international guidelines, and our Cochrane review concentrate on measured clinical excision margins (in whole number of centimetres) and Breslow thickness (stratified in 1 mm categories) as they relate to mortality and morbidity. This makes the studies more straightforward to measure and analyse. However, it seems biologically implausible that, for example, a 1.9 mm thick melanoma would behave significantly differently to a 2.1 mm thick melanoma, or a 3.9 mm thick melanoma would behave significantly differently to a 4.1 mm thick melanoma. Similarly it seems unlikely that a 2.1 cm margin, for example, would produce better outcomes than a 1.9 cm margin. Perhaps, partly by necessity, the trials are a little artificial in nature. It is probably impossible to make an accurate recommendation about the margin of excision required for each different melanoma in each individual person.

All but one study (Swedish study) had age restrictions and either excluded older participants or younger participants or (sometimes) both. It is not clear how this would affect melanoma management in older people.

There is little mention about 'informed consent' of participants or whether studies underwent appropriate 'medical research ethics review'. Most of the trials were designed 20 to 30 years ago, perhaps at a time when 'consent' and 'ethics' were not deemed of such paramount importance as they are today.

Potential biases in the review process

Several limitations of this systematic review need to be addressed. As with any meta-analysis there is the potential for publication bias to over-estimate differences in outcomes if studies identifying such differences are more likely to be published in peer-reviewed journals. However, our systematic search of the literature and the fact that we have contacted several 'leading authors and experts' in the field of melanoma management means that it is unlikely that we have missed any studies including substantial numbers of participants.

The total number of studies identified in this meta-analysis is modest simply because there are only five reported randomised trials which have examined melanoma excision margins. This has the effect of decreasing the statistical power to detect real differences in outcomes, thus reducing the robustness of our estimates. However, the total number of participants identified in this meta-analysis is moderately large with approximately 3300 participants in the pooled analysis. Therefore, although it is possible that inadequate

numbers were pooled for a clinically significant outcome difference, it suggests that if there is a true difference, then it is relatively small (of course acknowledging that small differences may be very important for individuals).

The five included studies are clinically heterogeneous (although they are not statistically heterogeneous). The range of excision margins deemed 'narrow' or 'wide' can dilute the effect size of potential outcome differences if only a subset of studies utilised an adequately narrow comparator. Thus, our meta-analysis may under-estimate potential true differences in outcome. Notably the absence of consistent excision margin definitions also limits our ability to make firm recommendations with regard to appropriate excision margins should any difference be detected.

The available data indicate that patients with thin melanomas are unlikely to benefit from very wide excisions. For example, of 762 (159 French, 244 Swedish, 359 WHO) participants with melanomas < 1 mm thick, roughly 380 (79 French, 123 Swedish, 171 WHO) were treated with a wide excision margin. As these patients are unlikely to benefit from this wide excision, it is possible that the results are diluted down and may mask a small effect. Similarly as 5 cm excision margins are now considered excessive (although not at the time of RCT study design), results from these trials may 'overwhelm' the results of our meta-analysis.

We have not examined in detail quality of life and cost-effectiveness in our analysis. These are valuable parameters for developing sensible clinical decisions and practice guidelines but there are limited published data which address these issues.

It is unlikely that a narrower margin would provide better survival outcomes than a wider excision (unless the procedures involved with wide excision resulted in excess mortality), so an important perspective of a review about melanoma margins could be to look for evidence of equivalence or non-inferiority of a narrower excision margin compared to a wider one. In this situation, the question could be posed "is a narrower margin not importantly worse than a wide one?" rather than superiority of a wider margin. However, the perspective of this review is not non-inferiority, since the aim was to quantify the uncertainty around the benefits and risks so that individuals can decide, with the support of health professionals, what the appropriate decision is for them. None of the included RCTs appear to have been designed or reported as a formal non-inferiority or equivalence study. Any future randomised trials should be sized to aim for a pre-specified precision for estimation of the potential inferiority in primary outcomes.

Agreements and disagreements with other studies or reviews

Three systematic reviews, each including meta-analysis, examining excision margins for primary cutaneous melanomas have previously been published.

The first of these (Lens 2002) included four RCTs.

The second (Haigh 2003) included three RCTs. Haigh et al concluded that

1. 'a surgical excision of no more than 2 cm around a melanoma of the trunk or extremities is adequate'; and
2. 'that surgical margins should be no less than 1 cm around the primary melanoma'.

Recently, Lens updated his meta-analysis to include all five currently published RCTs (Lens 2007). However, their conclusion that 'current evidence is insufficient to address the optimal excision margins for all types of melanomas' remained unchanged.

We performed our analysis differently to that of Lens (Lens 2007). Lens 2007 used rates based on the total observed events, which may be difficult to interpret because all the participants have not been followed up for the same time period (Cochrane handbook, section 9.2.6 Higgins 2008). We used hazard ratios for the primary analysis which summarise the average effect over the duration of follow-up. (Cochrane handbook, section 7.7.6 Higgins 2008). Our approach is in line with that recommended in the Cochrane handbook (sections 7.7.6 and 9.2.6), 'The most appropriate way of summarising time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard ratio'. However, in this case the results produced by both methods are similar.

AUTHORS' CONCLUSIONS

Implications for practice

None of the individual trials, nor our meta-analysis, has shown a statistically significant difference in overall survival between the two groups that were treated with narrow or wide excision margins. Current randomised trial evidence is insufficient to address optimal excision margins for primary cutaneous melanoma.

Despite this, however, numerous expert international committees have produced fairly consistent guidelines for melanoma excision margins.

It is important to determine whether the absence of any statistically significant overall survival difference in randomised studies (or meta-analyses thereof) conducted to date preclude the possibility that there may actually be a real but very small difference in survival for different margin widths (Johnson 2004). So far this question remains unanswered. There is a potential for causing harm if excision margins become excessively narrow. Narrow excision margins reduce surgical morbidity and complications, and the need for general anaesthesia, but should only be used if cure is not compromised.

Implications for research

Further randomised trials would be needed to clarify optimal excision margins for primary cutaneous melanoma. Any future tri-

als should be appropriately designed and powered to determine whether different subsets of Breslow thickness can be treated with different excision margins and, if so, the minimum optimal margins.

Current data suggest that 'narrow' margins produce similar outcomes to 'wider' margins so perhaps trials should compare different degrees of narrow excision margin, for example 1 versus 2 cm. However, an extremely large study would be required to demonstrate a lack of important difference between these different excision margins, because only a very small survival deficit (if any) would be acceptable. Similarly, a prospective trial for facial melanomas, perhaps comparing 0.5 cm and 1.0 cm excision margins, would be clinically very useful, but would likely require huge numbers of participants and resources.

In future trials, primary outcomes should focus on overall survival and report number of events. Authors should provide clear and consistent definitions of 'recurrences'. All trials should include and assess quality of life outcomes.

Individual patient data meta-analysis could be helpful in further investigating the impact of Breslow thickness on excision margins.

Access to detailed outcome data, broken down by Breslow thickness, would enhance the quality of future meta-analyses. This might improve the quality of treatment recommendations and subsequent care, and help researchers focus on the most appropriate clinical questions.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Balch 2001

Methods	Randomised trial. Multicentre, US, Canada, Denmark, South Africa. 93 surgeons practising in 77 centres Duration of trial: follow-up 10 years Generation of the randomisation sequence was made using the 'method of Zelan'. Written informed consent was obtained for all participants. The method of allocation concealment was unclear. The principal investigator reviewed all deaths and was blinded as to the surgical treatment involved The results were expressed as intention-to-treat and "treatment actually received" without difference (Dr Charles Balch, personal communication, Balch 1998)
Participants	In the 1993 report, the authors state that 486 participants were randomised (244 = 2 cm, 242 = 4 cm), of which 95.1% could be evaluated In the 1996 paper, the authors state that 470 participants were randomised (238 = 2 cm, 232 = 4 cm) In the 2001 paper, the authors state that 468 participants were randomised (238 = 2 cm, 230 = 4 cm). They also say 'more than 94% of the participants entered into the study were eligible and were able to be evaluated' and that 'there is now a 92% long-term follow-up of at least 5 years or until death' Participant age range was 18 to 81 years All participants had cutaneous melanoma of thickness 1.0 to 4.0 mm and no evidence of metastatic melanoma in regional lymph nodes or at distant sites All melanomas were confirmed histologically Lesions on trunk or proximal limbs Excision margins measured with a ruler. Lesions could be excised with a larger margin in one direction to create elliptical defect, thus easing closure. Underlying subcutaneous tissue, down to or including the underlying muscular fascia, was incorporated into the surgical specimen. Definitive resection was performed within 45 days after biopsy Participants who had had cancer previously (except for skin cancer) or who had received chemotherapy, radiotherapy, or any other adjunct to surgery were excluded. Participants with lentigo maligna melanoma were excluded
Interventions	Local excision with either a 2 or 4 cm margin
Outcomes	There were several primary outcome measures: 10 year disease-specific survival, 10 year first local recurrence, 10 year anytime local recurrence, 5 year overall survival, 5 year disease-free survival, 92 month local recurrence There were several secondary outcome measures: skin grafting, hospital stay, wound infection rate, wound dehiscence rates
Notes	The trial was published as 3 reports: 1993, 1996, 2001 The number of participants randomised is different in these reports: 486 in the 1993 report, 470 in the 1996 report, and 468 in the 2001 report Local recurrence defined as a biopsy-proven first recurrence within 2 cm of the scar 'Each participant was also randomly assigned to receive ELND (elective lymph node

Balch 2001 (*Continued*)

	dissection) or observation of the regional lymph nodes with delayed lymph node dissection only if clinically indicated.' 'Participants receiving ELND were evenly distributed between the two treatment arms involving surgical margins, so any survival differences that may result from ELND would not influence the survival outcome from the surgical margin issue'

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Incomplete outcome data addressed? All outcomes	Unclear	Unclear
Free of selective reporting?	Yes	Adequate
Free of other bias?	Unclear	Unclear

Cascinelli 1998

Methods	Randomised trial. Multicentre, multinational Duration of trial: follow-up 12 years Recruitment from 1980 to 1985 The random allocation was performed by a co-ordinating centre which sent each participating centre a series of sealed envelopes, each containing a randomisation number and the treatment to be assigned. A copy of the randomisation series was kept by a secretariat so the randomisation procedure of each centre could be checked The method of allocation concealment was unclear (as per Cochrane handbook, see main text for explanation). There was insufficient data to determine who was blinded. The analysis was not intention-to-treat
Participants	703 participants were randomised, of which 612 (87%) were evaluated Of these 612, 305 were randomised to the 1 cm excision group and 307 to the 3 cm excision group Participants had to be aged 65 or under All participants had cutaneous melanoma 2 mm or less in thickness Melanomas on trunk or limbs (except fingers or toes). Not face All melanomas were confirmed histologically. 3 representative path slides of each primary tumour were reviewed by a panel of 5 pathologists, chaired by one of the authors, in order to ensure a uniform evaluation of the prognostic criteria Wide excision was defined as a cutaneous incision made at least 3 cm from the grossly visible margins of the melanoma or from the scar if the primary melanoma had already been biopsied; the excisions had to be 1 to 2 cm wider in the subcutaneous fat extending to muscle fascia. Narrow excisions were performed according to the same technique; the only difference was that the cutaneous incisions were made 1 cm from the visible

Cascinelli 1998 (*Continued*)

	margins of the primary melanoma. The margins were measured by the surgeon at the time of the operation. Definite surgical treatment was to be performed within 6 weeks of the primary diagnostic procedure Participants with melanoma satellites, with multiple primary melanomas, with a history of cancer, who for any reason could not be followed-up on a regular basis, with no adequate histological documentation, and excision biopsy performed more than 6 weeks before definitive treatment were not eligible
Interventions	Local excision with either a 1 or 3 cm margin
Outcomes	There were many primary outcome measures, all of which were survival and recurrence rates for different time points: 12 year overall survival, 8 year actuarial survival rate, 8 year disease-free survival rate, 4 year actuarial survival rate, 12 year local recurrence, 8 year (total combined) disease relapse, 8 year local recurrence, 8 year in-transit metastases, 8 year regional nodal metastases, 8 year distant metastases, 4 year disease relapse, 4 year local recurrence, 4 year in-transit metastases, 4 year regional nodal metastases, and 4 year distant metastases There were no 'quality of life' outcome measures
Notes	The trial was published as 3 reports: 1988, 1991, and 1998 The 1988 paper states that 'local recurrences and in-transit and nodal metastases were defined as in the TNM staging system (IUAC, 1978)' [The TNM classification of malignant tumours is the global standard in cancer staging that describes the extent of cancer in a patient's body. T describes the primary tumor, N describes regional lymph nodes that are involved, and M describes distant metastasis] The 1991 paper states that local recurrence was defined as cutaneous or subcutaneous nodules in scar or within 1 cm of scar Concimitant treatment was permitted with guidelines given for treatment in the first 5 years of follow-up: 1. Local recurrence to be removed by wide local excision within 4 weeks of diagnosis; 2. If nodal metastases, standard axillary/inguino-iliac node dissection within 4 weeks; 3. Adjuvant treatment could be given for after surgery for nodal metastases (defined pre-trial); and 4. Distant metastases to be treated with chemotherapy, in the first instance, dacarbazine

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Incomplete outcome data addressed? All outcomes	Unclear	Unclear
Free of selective reporting?	Yes	Adequate

Cascinelli 1998 (*Continued*)

Free of other bias?	Unclear	Unclear

Cohn-Cedermark 2000

Methods	Randomised trial. Multicentre, Sweden, 5 regional oncologic centres, 39 clinics (38 hospitals) recruited Duration of trial: follow-up median 11 years OS, 8 RFS Recruitment from 1982 to 1991 The random allocation to the 2 treatment groups was done using balanced lists. At 3 of the trial centres, separate lists for each participating hospital were used. At the remaining 2 centers, there was no stratification by hospital. The method of allocation concealment was adequate with the personal data of each randomised participant and the tumour thickness noted on the list before the assigned treatment was revealed. There was insufficient data to determine who was blinded. The analysis was intention-to-treat
Participants	989 participants were randomised, 476 to the 2 cm excision group and 513 to the 5 cm excision group There was no restriction on participant age Participants who met the inclusion criteria had histologically proven, cutaneous, melanoma measuring > 0.8 mm and < = 2.0 mm in thickness with a trunk or extremity location (except hands and feet) All melanomas were confirmed histologically Melanomas on trunk or extremity location (except hands and feet). Not face Definite surgical treatment was to be performed within 6 weeks of the primary diagnostic procedure (i.e. all initially received 2 cm margin, then those randomised to wide excision received secondary procedure within 6 weeks) Participants with melanoma satellites or metastatic disease were not eligible, nor were participants with previous malignant disease (except basal cell carcinoma)
Interventions	Local excision with either a 2 or 5 cm margin
Outcomes	There were several primary outcome measures: OS (overall survival) at median 11 years follow-up, 10 year OS, RFS (recurrence-free survival) at median 8 years follow-up, 5 year RFS, 10 year RFS, OS at median 5.8 years follow-up, and RFS at median 4 years follow-up There were no 'quality of life' outcome measures
Notes	The trial was published as 2 reports: 1996 and 2000 Local recurrence was defined as a recurrence in the 'scar or transplant'. Other forms of recurrence are not defined The standard salvage treatment after locoregional disease recurrence was surgery. After repeated locoregional recurrences, some participants were treated with limb perfusion. In the event of distant dissemination, chemotherapy was given at the discretion of the respective physician

Risk of bias

Item	Authors' judgement	Description

Cohn-Cedermark 2000 (*Continued*)

Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Incomplete outcome data addressed? All outcomes	Yes	Adequate
Free of selective reporting?	Yes	Adequate
Free of other bias?	Unclear	Unclear

Khayat 2003

Methods	Randomised trial. Multicentre, European Duration of trial: median follow-up of 192 months (range 2 to 228) The method of generation of the randomisation sequence was unclear. The method of allocation concealment was unclear. There was insufficient data to determine who was blinded. The study was not intention-to-treat analysis
Participants	337 participants randomised, 167 to the 2 cm group and 170 to the 5 cm group 326 participants evaluated, 161 (of 167) in the 2 cm group and 165 (170) in the 5 cm group Participants were younger than 70 years Maximum tumour thickness was 2 mm, stage 1 disease as defined by TMN criteria All melanomas were confirmed histologically Lesions on trunk, limbs, head, and neck, excluding fingers, toes, and nails Before entry, all participants underwent clinical examination, CXR (chest x-ray), liver ultrasound Resection was performed within a month of the initial biopsy (if needed to obtain the overall 2 or 5 cm margin). Excisions extended down to the muscle fascia. Lymph node dissections not performed All biopsy specimens reviewed to confirm tumour thickness and histological classification Exclusion criteria: age 70 years or over, melanoma on fingers, toes, and nails, melanomas arising from melanosis, lentigo, acral lesions
Interventions	Local excision with either a 2 or 5 cm margin
Outcomes	10 year overall survival, 10 year disease-free survival, number of deaths at 192 months (median follow-up), number of participants free of disease at 192 months (median follow-up), number of tumour recurrences at 192 months (median follow-up), 5 year overall survival, 5 year disease-free survival, number of disease relapse at 50 months, number of deaths at 50 months There were no 'quality of life' outcome measures
Notes	The trial was published as 2 reports: follow-up at 5 years (1993) and at 192 months (2003) The number of participants randomised is different in these reports: 319 in the 1993 abstract and 337 (326 evaluated) in the 2003 report

Khayat 2003 (*Continued*)

	Local disease recurrence defined as recurrence within 2 cm of the scar In-transit metastases was defined as disease recurrence between the primary tumour site and the regional lymph node Certain concomitant treatment was permitted. Local or regional tumours that recurred were removed surgically. Metastatic tumours were treated with chemotherapy or biochemotherapy A second randomisation allocated the participant to either 12 months of adjuvant treatment with Isoprinosine or to no adjuvant treatment. Participant characteristics, including surgical margins were balanced between the 2 groups based on the immunotherapy randomisation. This second randomisation to receive or not to receive Isoprinosine did not appear to affect the outcome of these participants. The median survival periods with or without the drug were 190 months and 192 months respectively (P = 0.9) and the disease-free survival periods were 149.5 months and 153.3 months respectively (P = 0.89)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Incomplete outcome data addressed? All outcomes	Unclear	Unclear
Free of selective reporting?	Yes	Adequate
Free of other bias?	Unclear	Unclear

Thomas 2004

Methods	Randomised trial. Multicentre, UK, and Poland Duration of trial: median follow-up 60 months Recruitment from 1993 to 2001 Permuted blocks of random size were used for randomisation, and the allocation ratio was 1:1. Randomisation was performed by telephone at a central site and the method of allocation concealment was adequate. There was insufficient data to determine who was blinded. The analysis was intention-to-treat
Participants	900 participants were randomised, 453 to the 1 cm excision group and 447 to the 3 cm excision group Eligible participants had to be aged 18 or over Single, primary, localised cutaneous melanoma 2 mm or greater in thickness All melanomas were confirmed histologically Site of lesion was trunk or limbs (excluding the palms of the hands or the soles of the feet) Participating surgeons chose 1 of 2 primary treatment approaches. The primary tumor could be excised before randomisation, with either a 1 mm or a 1 cm margin to confirm

	the diagnosis and determine the thickness of the lesion. The participants were then randomly assigned to receive a 1 or 3 cm margin after the 1 mm primary excision or to receive no further treatment or an additional 2 cm margin after the 1 cm primary excision. The trial surgery was to be performed within 45 days after the primary excision, and all excisions were to extend to or include the deep fascia Sentinal lymph node biopsy was not performed Participants with a history of cancer (other than basal cell carcinoma) or on immuno-suppressive therapy were not eligible
Interventions	Local excision with either a 1 or 3 cm margin
Outcomes	There were several primary outcome measures: overall survival, disease-free survival and melanoma recurrence-locoregional (defined as first-event local or in-transit recurrence combined with nodal recurrence). Number of events (that is deaths or recurrences) were given for all of these outcomes Secondary outcome measures included Surgical complications rates. Data on the quality of life were collected from a sample of 426 participants and are reported separately (Newton-Bishop 2004
Notes	Local recurrence defined as a recurrence within 2 cm of the scar or graft. In-transit recurrence was defined as a recurrence from beyond the first 2 cm of the scar or graft to the regional nodes. All locoregional recurrences were detected clinically and confirmed by biopsy. These end points were combined in the final analysis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Incomplete outcome data addressed? All outcomes	Unclear	Unclear
Free of selective reporting?	Yes	Adequate
Free of other bias?	Unclear	Unclear

Characteristics of excluded studies *[ordered by study ID]*

We did not exclude any randomised trial which compared different width excision margins.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Characteristics of ongoing studies *[ordered by study ID]*

Ringborg 2005

Trial name or title	Randomised trial of a resection margin of 2 versus 4 cm for cutaneous malignant melanoma with a tumour thickness of more than 2 mm
Methods	RCT
Participants	936 participants with primary cutaneous melanomas with a tumor thickness above 2.0 mm
Interventions	Excision margin of 2 cm compared with excision margin of 4 cm
Outcomes	Results are awaited
Starting date	Trial recruitment 1992 to 2004
Contact information	Prof U Ringborg
Notes	

DATA AND ANALYSES

Comparison 1. Narrow vs wide margin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	5		HR (Fixed, 95% CI)	Subtotals only
1.1 All available data	5	3297	HR (Fixed, 95% CI)	1.04 [0.95, 1.15]
1.2 Excluding estimates based on actuarial rate at specific time point	4	2685	HR (Fixed, 95% CI)	1.03 [0.88, 1.21]
2 Recurrence-Free Survival	5		HR (Fixed, 95% CI)	Subtotals only
2.1 All available data	5	3297	HR (Fixed, 95% CI)	1.13 [0.99, 1.28]
2.2 Excluding estimates based on actuarial rate at specific time point	2	1889	HR (Fixed, 95% CI)	1.13 [0.97, 1.32]

Comparison 2. Death versus Breslow thickness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death			Other data	No numeric data

Analysis 1.1. Comparison 1 Narrow vs wide margin, Outcome 1 Overall survival.

Review: Surgical excision margins for primary cutaneous melanoma

Comparison: 1 Narrow vs wide margin

Outcome: 1 Overall survival

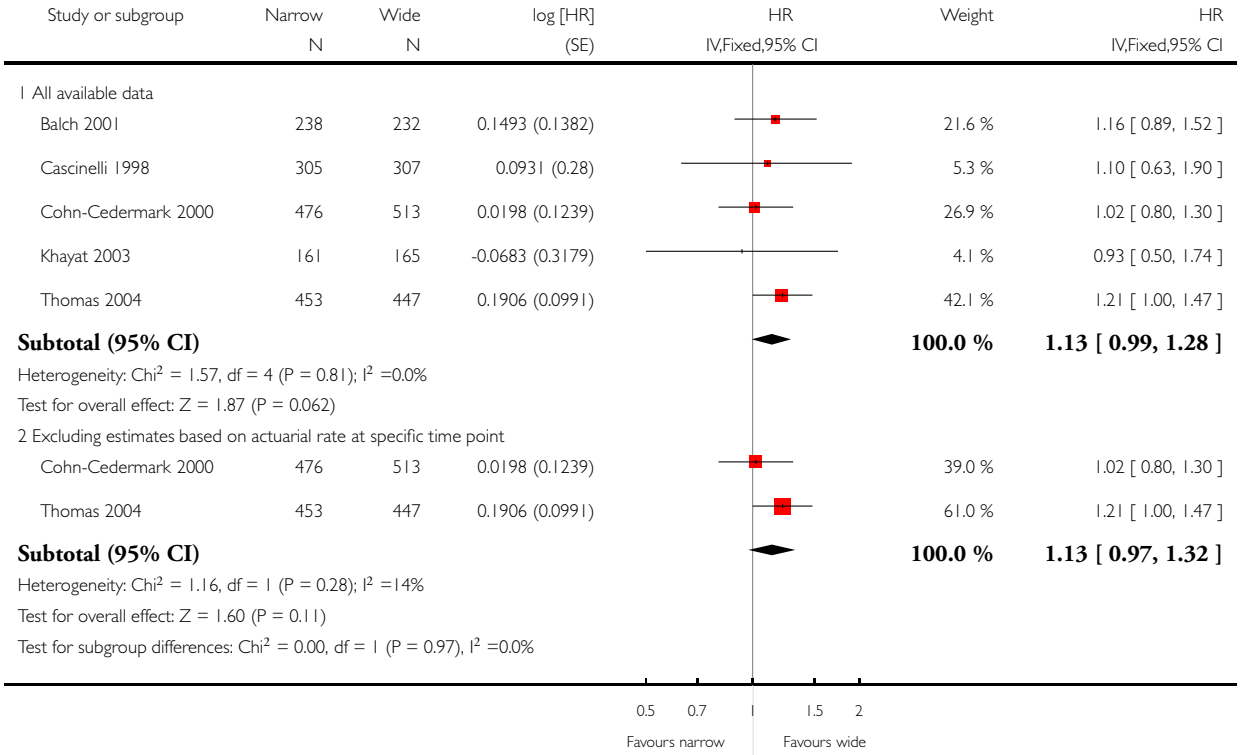
Study or subgroup	Narrow N	Wide N	log [HR] (SE)	HR IV,Fixed,95% CI	Weight	HR IV,Fixed,95% CI
1 All available data						
Balch 2001	238	232	0.4237 (0.2944)		2.9 %	1.53 [0.86, 2.72]
Cascinelli 1998	305	307	0.0303 (0.0648)		60.3 %	1.03 [0.91, 1.17]
Cohn-Cedermark 2000	476	513	-0.0408 (0.1283)		15.4 %	0.96 [0.75, 1.23]
Khayat 2003	161	165	0.1493 (0.2561)		3.9 %	1.16 [0.70, 1.92]
Thomas 2004	453	447	0.0677 (0.1199)		17.6 %	1.07 [0.85, 1.35]
Subtotal (95% CI)					**100.0 %**	**1.04 [0.95, 1.15]**
Heterogeneity: Chi^2 = 2.35, df = 4 (P = 0.67); I^2 =0.0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
2 Excluding estimates based on actuarial rate at specific time point						
Balch 2001	238	232	0.0953 (0.504)		2.6 %	1.10 [0.41, 2.95]
Cohn-Cedermark 2000	476	513	-0.0408 (0.1283)		40.6 %	0.96 [0.75, 1.23]
Khayat 2003	161	165	0.1493 (0.2561)		10.2 %	1.16 [0.70, 1.92]
Thomas 2004	453	447	0.0677 (0.1199)		46.5 %	1.07 [0.85, 1.35]
Subtotal (95% CI)					**100.0 %**	**1.03 [0.88, 1.21]**
Heterogeneity: Chi^2 = 0.64, df = 3 (P = 0.89); I^2 =0.0%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 =0.0%						

Analysis 1.2. Comparison 1 Narrow vs wide margin, Outcome 2 Recurrence-Free Survival.

Review: Surgical excision margins for primary cutaneous melanoma

Comparison: 1 Narrow vs wide margin

Outcome: 2 Recurrence-Free Survival



Analysis 2.1. Comparison 2 Death versus Breslow thickness, Outcome 1 Death.

Death

Balch 2001	1.0 to 2.0	30/148 (20%)	21/142 (15%)
Balch 2001	2.1 to 3.0	24/67 (36%)	19/62 (31%)
Balch 2001	3.1 to 4.0	12/23 (52%)	8/26 (31%)
Balch 2001	Total	66/238 (28%)	48/230 (21%)
Cohn-Cedermark 2000	< 1 mm	44/121 (36%)	29/123 (24%)
Cohn-Cedermark 2000	1 to 2 mm	144/345 (42%)	166/387 (43%)
Cohn-Cedermark 2000	> 2 mm	8/10 (80%)	1/1 (100%)

Death (*Continued*)

Cohn-Cedermark 2000	Total	196/476 (41%)	196/511 (38%)

APPENDICES

Appendix 1. Cochrane Library search strategy

#1(melanoma):ti,ab,kw
#2MeSH descriptor Melanoma explode all trees
#3(#1 OR #2)
#4(excis* or margin* or surg* or remov*):ti,ab,kw
#5(#3 AND #4)
#6SR-SKIN
#7(#5 AND NOT #6)

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. melano$.mp.
12. exp *MELANOMA/dt, su [Drug Therapy, Surgery]
13. 11 or 12
14. (excis$ or margin$ or surg$ or remov$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. *SURGERY/mt, su [Methods, Surgery]
16. 14 or 15
17. 16 and 13 and 10

Appendix 3. EMBASE search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (assign$ or allocat$).mp.

8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. melano$.mp.
15. exp MELANOMA/co, si, su, th [Complication, Side Effect, Surgery, Therapy]
16. (excis$ or margin$ or surg$ or remov$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
17. exp MINIMALLY INVASIVE SURGERY/ or exp MINOR SURGERY/ or exp CANCER SURGERY/ or exp SURGERY/
18. 14 or 15
19. 16 or 17
20. 18 and 19
21. 13 and 20

Appendix 4. CINAHL search strategy

1 skin ADJ cancer
2 SKIN-NEOPLASMS.DE. OR MELANOMA.W..DE.
3 su.DE.
4 skin ADJ tumour$ OR skin ADJ tumor$
5 skin ADJ neoplasms
6 SKIN-NEOPLASMS#.DE. OR MELANOMA#.W..DE.
7 1 OR 2 OR 4
8 surg$.TI.
9 excis$ OR margin$
10 3 OR 8 OR 9
11 7 AND 10
12 PT=CLINICAL-TRIAL OR PT=PRACTICE-GUIDELINES OR PT=RESEARCH OR PT=REVIEW OR PT=STANDARDS OR PT=STATISTICS OR PT=SYSTEMATIC-REVIEW
13 random$
14 randomised ADJ controlled ADJ trials
15 (double OR single OR treble OR triple) NEAR blind$
16 Clinical-Trials.DE.
17 12 OR 14 OR 14 OR 15 OR 16
18 11 AND 17

Appendix 5. AMED search strategy

No. 1, Search term: “melanoma” (Results 119)
No. 2, Search term: “MELANOMA#.W..DE. OR SKIN-NEOPLASMS#.DE.” (Results 94)
No. 3, Search term: “skin ADJ cancer” (Results 19)
No. 4, “1 OR 2 OR 3” Results 174)
No. 5, Search term: “surg$ OR excis$ OR margin$” (Results 7862)
No. 6, Search term: “4 AND 5”(Results 24)

Appendix 6. LILACS search strategy

We performed the following two searches:
((skin cancer) or “SKIN CANCER/SU”) or “SKIN NEOPLASMS/SU” [Words] or “MELANOMA” [Words] and “SURGERY” [Words]
((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words] and melanoma [Words] and surgery or cirugia or bisturi or quirurgico or eliminacion or margen or borde or linea or escision [Words]

Appendix 7. Science Citation Index search strategy

#1 23,702 TS=(((skin or cutaneous) same (cancer* or neoplasm* or tumour* or tumor* or melanoma* or carcinoma*)))Timespan=1981-2004
#2 >100,000 TI=(surg*) Timespan=1981-2004
#3 24,159 TI=(excis* or margin*) Timespan=1981-2004
#4 >100,000 #2 or #3 Timespan=1981-2004
#5 566 #1 and #4 Timespan=1981-2004

Appendix 8. Adverse events search strategy

1. exp MELANOMA/su [Surgery]
2. excis$.mp.
3. margin$.mp.
4.1 and 2 and 3

WHAT'S NEW

Last assessed as up-to-date: 2 August 2009.

9 November 2009	Amended	Minor correction.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 4, 2009

4 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MS is listed as the first/lead author; other authors are listed alphabetically.

The following contributions will be made by the authors stated:

Link with editorial base: MS

Draft the protocol: MS, DAB, TH, NT

Comment on draft protocol: MS, DAB, DB, TH, PH, SH, NT, JT

Run search for trials: MS, AF

Identify relevant titles and abstracts from searches: MS, AF

Obtain copies of trials: MS, AF

Select which trials to include: MS, AF

Extract data from trials: MS, AF

Enter data into RevMan: SH

Carry out the analysis: SH

Interpret the analysis: MS, DAB, AF, SH, JT

Draft the final review: MS, DAB, DB, AF, TH, SH, JT

Comment on final draft: MS, CB, DAB, DB, AF, TH, SH, ML, JT

Update the review: MS, DAB, AF, SH

Take overall responsibility for the review: MS

DECLARATIONS OF INTEREST

Charles Balch who is one of the co-authors of this review was also an author on the Intergroup study.

SOURCES OF SUPPORT

Internal sources

- University Hospitals of Leicester NHS Trust, UK.
- Case Western Reserve University, USA.
- Lancaster University, UK.

External sources

- AHRQ grant #T32 HS00059-09, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to perform a subgroup analysis based on Breslow thickness of melanoma and a subgroup analysis based on body site of melanoma, however there was insufficient data to perform either of these analyses.

In the protocol, we mentioned only clinical margins. However, in the final review we though it important to clarify that the RCTs only measured clinical margins and not histological margins.

In the protocol, we mentioned 'short-term' (1 to 2yrs) analysis. However, none of the RCTs published such short-term data so we have could not analyse it in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Melanoma [mortality; pathology; *surgery]; Randomized Controlled Trials as Topic; Skin Neoplasms [mortality; pathology; *surgery]

MeSH check words

Humans