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Systematic or Meta-analysis Studies

Surgical excision margins in primary cutaneous melanoma: A meta-analysis and Bayesian probability evaluation

Keith Wheatley [a], Jayne S. Wilson [a], Piers Gaunt [a], Jerry R. Marsden [b,*]

[a] Cancer Research UK Clinical Trials Unit, Institute of Cancer & Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom
[b] Skin Oncology Service, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, United Kingdom

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ABSTRACT

Background: Surgery is the only curative treatment for primary cutaneous melanoma, therefore it is important to determine excision margins that minimise risk of local recurrence, distant recurrence and death.
Methods: MEDLINE, EMBASE and Cochrane CENTRAL were searched from 2009 to 2015. Inclusion criteria were: population/setting – patients with primary melanoma; comparison – narrow versus wide margins; outcomes – overall survival, melanoma-specific survival, recurrence-free survival, and loco-regional recurrence; design – randomized controlled trials (RCTs). Results were pooled using meta-analysis and data explored using likelihood Bayesian probability plots.
Results: Six RCTs with 4233 patients were included. Narrow margins were defined as 1 or 2 cm of clinically normal skin around the melanoma; wide margins as 3, 4 or 5 cm. Hazard ratios (HR) were as follows (HR > 1 indicates wide margin better): overall survival 1.09 (95% CI 0.98–1.22; $p = 0.1$); melanoma-specific survival 1.17 (CI 1.03–1.34; $p = 0.02$); recurrence-free survival 1.08 (CI 0.97–1.20; $p = 0.2$); loco-regional recurrence 1.10 (CI 0.96–1.26; $p = 0.2$), with no evidence of heterogeneity between trials for any end point or within subgroup analyses. There was an 94% probability that overall survival was worse with a narrow margin and a 43% probability that it was more than 10% worse in proportional terms (i.e. HR > 1.1). Probabilities that narrow margins were worse were 99%, 92% and 92% for melanoma-specific survival, recurrence-free survival and loco-regional recurrence respectively.
Conclusions: Contrary to recommendations in several national guidelines that narrow margins are safe, this systematic review and meta-analysis provides evidence that a narrow margin may lead to a worse outcome than a wide margin.

Introduction

Surgery remains the only curative treatment for primary cutaneous melanoma [1]. Surgical treatment has conventionally included a margin of surrounding normal-looking skin. The purpose of this margin is both to completely remove the primary melanoma, and to completely remove any micro-metastases that might be present in the surrounding skin. The size of the margin required to minimise risk of recurrence and death has long been a subject of debate.

Despite five randomized controlled trials [2–6] and three recent systematic reviews [7,9] the optimum excision margins for primary cutaneous melanoma remain unclear. The general consensus of the reviews is that there is little difference in outcome between narrow (1 or 2 cm) and wide (3, 4 or 5 cm) margins but that there is insufficient evidence to prove that narrow margins are safe. Despite this uncertainty, several national guidelines [10–15] (Table 1) published between 2005 and 2010 make clear recommendations that a margin of 2 cm is sufficient for melanomas of greater than 2.0 mm Breslow thickness and that a margin of 1 cm is sufficient for melanomas 1.0–2.0 mm in thickness. The view that current evidence supports these margins is not universally held [10].

With the publication of a sixth RCT [16] and updated data from a previously published trial [6,17] there is a need for an updated systematic review of primary cutaneous melanoma surgical margins. We have used standard meta-analysis methods, and for the first time, a probability-based analysis of the data.

* Corresponding author.

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Table 1
Summary of recommendations on margin width in National Guidelines.

Country	Surgical margin recommendation (cm) according to Breslow thickness (mm)		
	1.01–2.0 mm	2.01–4.0 mm	>4.0 mm
UK 2010 [10]	1–2 cm	2–3 cm	3 cm
USA 2012 [11]	1–2 cm	2 cm	2 cm
Australia 2008 [12]	1–2 cm	1–2 cm	2 cm
German 2008 [13]	1 cm	2 cm	2 cm
Swiss 2005 [14]	1 cm	2 cm	2 cm
Dutch 2012 [15]	1 cm	2 cm	2 cm

Methods

The Cochrane review on this topic [8] was well conducted with wide ranging searches up to 2009 and appropriate systematic review methods utilized. It was thought unnecessary to repeat this work so our search covered the period from 2009 to August 2015. This review was conducted according to a study protocol, which is available in the Supplementary material and reported according to the PRISMA checklist [18]. Bibliographic databases – MEDLINE, EMBASE, and Cochrane CENTRAL – were searched to identify published studies. Search terms, combined with an RCT filter, were "melanoma" and "surgery". No language restrictions were applied. Identified reports were assessed for eligibility using the title and abstract by a single reviewer. Investigators were contacted if necessary and citations of relevant papers were scrutinized. We also searched the research register ClinicalTrials.gov and the American Society of Clinical Oncology (ASCO) conference proceeding abstract database up to August 2015 for ongoing and unpublished trials.

Studies were included if they met the following inclusion criteria: population/setting – patients with primary cutaneous melanoma; intervention – narrow surgical margin; comparator – wide surgical margin; outcomes – overall survival, melanoma specific survival, recurrence-free survival, and local-regional recurrence; design – randomized controlled trials (RCTs) or systematic reviews. Publication bias was explored using funnel plots [19].

Study characteristics, such as the description of the patients included in the trials (age, site of melanoma, prior melanoma treatments/biopsy procedures etc.), intervention and comparator treatments were extracted and entered onto a pre-designed data extraction form by one reviewer and checked by a second reviewer. Outcome data for the meta-analysis were extracted independently by two reviewers, recording the source of data and reasons for using specific data points. Study quality was assessed in terms of selection, performance, attrition and detection bias and was undertaken independently by two reviewers.

Statistical analysis

Fixed effect meta-analyses were performed on the following: overall survival, melanoma-specific survival, non-melanoma deaths, recurrence-free survival, and loco-regional recurrence (the latter two as defined by the authors for each trial). Where possible, data was taken from univariate analysis in preference to multivariate analysis. Time-to-event data were extracted using standard methods from Tierney and Parmar [20,21]: observed minus expected (O–E) number of events and its variance were calculated from the hazard ratio, confidence interval (CI), *p*-value and survival proportions/number of events (with the variance being estimated as one quarter the total number of events if the latter was the only information available) where available (Table A1). Heterogeneity was assessed using Chi-squared [19].

Two subgroup analyses were performed: by randomized comparison (1 cm versus 3 cm margins; 2 cm versus 4 or 5 cm margins) and by Breslow thickness of the melanoma (<2 mm; ⩾2 mm). Chi-squared tests for interaction between subgroups were performed [19].

Results are also presented using probability plots. This is termed "likelihood Bayesian" since it involves plotting the posterior probability distribution obtained from the data, with the use of a vague prior (i.e. no assumptions about prior information are made) [22,23].

Results

Trials and patients

The updated search (see PRISMA diagram; Fig. 1) identified one recent randomized trial [16] and an updated report of an already published trial [17]. Adding this to the five RCTs identified in the Cochrane review [8] gave a total of six completed trials involving 4249 patients; trial sizes ranged from 326 to 989 patients.

The margins compared were: 1 cm versus 3 cm [2,6]; 2 cm versus 4 cm [4,16]; 2 cm versus 5 cm [3,5]. Three trials included patients with tumours ⩽2.0 mm thick [2,3,5]; two included patients with tumours >2.0 mm thick [6,16]; one included patients with tumours between 1.0 and 4.0 mm thick [4] although the results split by ⩽2.0 mm and >2.0 mm were reported. Data on loco-regional recurrence and recurrence-free survival were reported for all six trials; data on overall survival may have been reported for all six trials, though there is some uncertainty regarding the Intergroup trial [4,24] (see Discussion); melanoma-specific survival was reported in four trials [3,4,6,16]. The characteristics of all trials are reported in Table 2.

In addition to the completed trials, one ongoing trial called the MelMarT Melanoma Margins Trial, NCT01457157 (previously registered as NCT02385214) was identified [25]. This trial compares 1 cm margins with 2 cm margins, both of which would be classed as narrow margins in this review. The trial started in 2014 and initially aims to recruit 400 patients for feasibility. If continued, it is expected to complete in 2029.

Risk bias of included studies

For all six RCTs, study quality was generally good, with better reporting in the most recent publications (Table 3). The Intergroup [4] and European/French [5] trials failed to describe their randomisation procedures and it was unclear whether allocation was concealed. Three trials (Swedish I [3], European [5], Swedish II [16]) reported that patients who had a 2 cm margin excision at their initial biopsy did not have further surgery if allocated a 2 cm margin. This means that some patients in the narrow group may have had surgery 4–8 weeks prior to patients in the wide group and also that they may not have had an excision to muscle fascia, a standard requirement for treating melanoma, as this would not be usual in a diagnostic excision biopsy procedure. Follow-up was good in all trials. Only the Intergroup trial [4] reported blinding of outcome assessors. A funnel plot for overall survival (not shown) indicated slight asymmetry with small trials missing in favour of narrow margins. We would assume had these been available that the trials would have been reported as they would be considered favourable. It is worth noting that Cochrane recommends a minimum of 10 trials to produce a reliable funnel plot [19].

Overall survival

The hazard ratio for overall survival (6 trials) was 1.09 (95% CI 0.98–1.22; $p = 0.1$), with no evidence of heterogeneity between the trials (test for heterogeneity: $p = 0.7$) (Fig. 2a). If the Intergroup