International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (999-1004), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Epidemiological and Etiology Review of Melanoma Worldwide: Systematic Review

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Abstract: **Surgical treatment is the only alleviative treatment for main cutaneous cancer malignancy, for that reason it is necessary to determine excision margins that reduce risk of regional reoccurrence, far-off reoccurrence and death.6 RCTs with 4233 patients were included. Narrow margins were defined as 1 or 2 cm of medically regular skin around the melanoma; large margins as 3, 4 or 5 cm. Risk ratios (HR) were as follows (HR > 1 shows broad 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 reoccurrence 1.10 (CI 0.96-- 1.26; p = 0.2), with no evidence of heterogeneity in between trials for any endpoint or within subgroup analyses. There was an 94% probability that overall survival was even worse with a narrow margin and a 43% likelihood that it was more than 10% even worse in proportional terms (i.e. HR > 1.1). Possibilities that narrow margins were even worse were 99%, 92% and 92% for melanoma-specific survival, recurrence-free survival and loco-regional re-occurrence respectively.The main aim of this systematic review is to provide an updated review of cutaneous melanoma surgical margins We have used standard meta-analysis methods, and for the first time, a probability-based analysis of the data.**

Keywords: **Surgical treatment, melanoma, systematic review, methods.**

1. INTRODUCTION

Occurrence rate of cutaneous melanoma (CM) has actually gradually increased in Caucasian populations worldwide, in both ladies and men and in all age groups. Regardless of a recent flattening of this pattern, CM has actually turned into one of the most regular cancers in fair-skinned populations[(1)].

As for all cancers, the incident of CM is the outcome of the interaction in between host and environmental factors. While the main constitutional and ecological risk aspects for CM are well known[(2)], it stays unclear how these danger elements communicate to determine the physiological site and histological type of the developing tumor.

Direct exposure to the sun is the most essential environmental reason for skin cancer, with the wavelength for ultraviolet radiation connected with advancement of the disease[(3)]. The wavelengths for ultraviolet radiation variety in between 100 nm and 400 nm and are broadly categorized into ultraviolet A light (315-400 nm), ultraviolet B (280-315 nm), and ultraviolet C (100-280 nm). All ultraviolet C and most ultraviolet B wavelengths are blocked by the dizzying ozone layer. A fraction of ultraviolet B and all ultraviolet A reaches the Earth's surface.

Surgery remains the only curative treatment for primary cutaneous melanoma [(4)]. Surgical treatment has actually traditionally included a margin of surrounding normal-looking skin. The pur- position of this margin is both to entirely get rid of the main melanoma, and to completely eliminate any micro-metastases that might be present in the surrounding skin. The size of the margin needed to decrease danger of recurrence and death has actually long been a topic of debate.

Despite 5 randomized regulated trials [5-9] and 3 current systematic evaluations [10,11] the optimum excision margins for primary cutaneous melanoma remain unclear. The basic consensus of the reviews is that there is little difference in outcome between narrow (1 or 2 cm) and broad (3, 4 or 5 cm) margins but that there is insufficient proof to prove that narrow margins are safe.

The main aim of this systematic review is to provide an updated review of cutaneous melanoma surgical margins We have used standard meta-analysis methods, and for the first time, a probability-based analysis of the data.

2. METHODOLOGY

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.

3. RESULTS AND DISCUSSION

The updated search (see PRISMA diagram; Fig. 1) determined one recent randomized trial [12] and an upgraded report of a currently released trial [13]. Including this to the 5 RCTs identified in the Cochrane evaluation [14] offered an overall of 6 completed trials including 4249 patients; trial sizes varied from 326 to 989 patients.

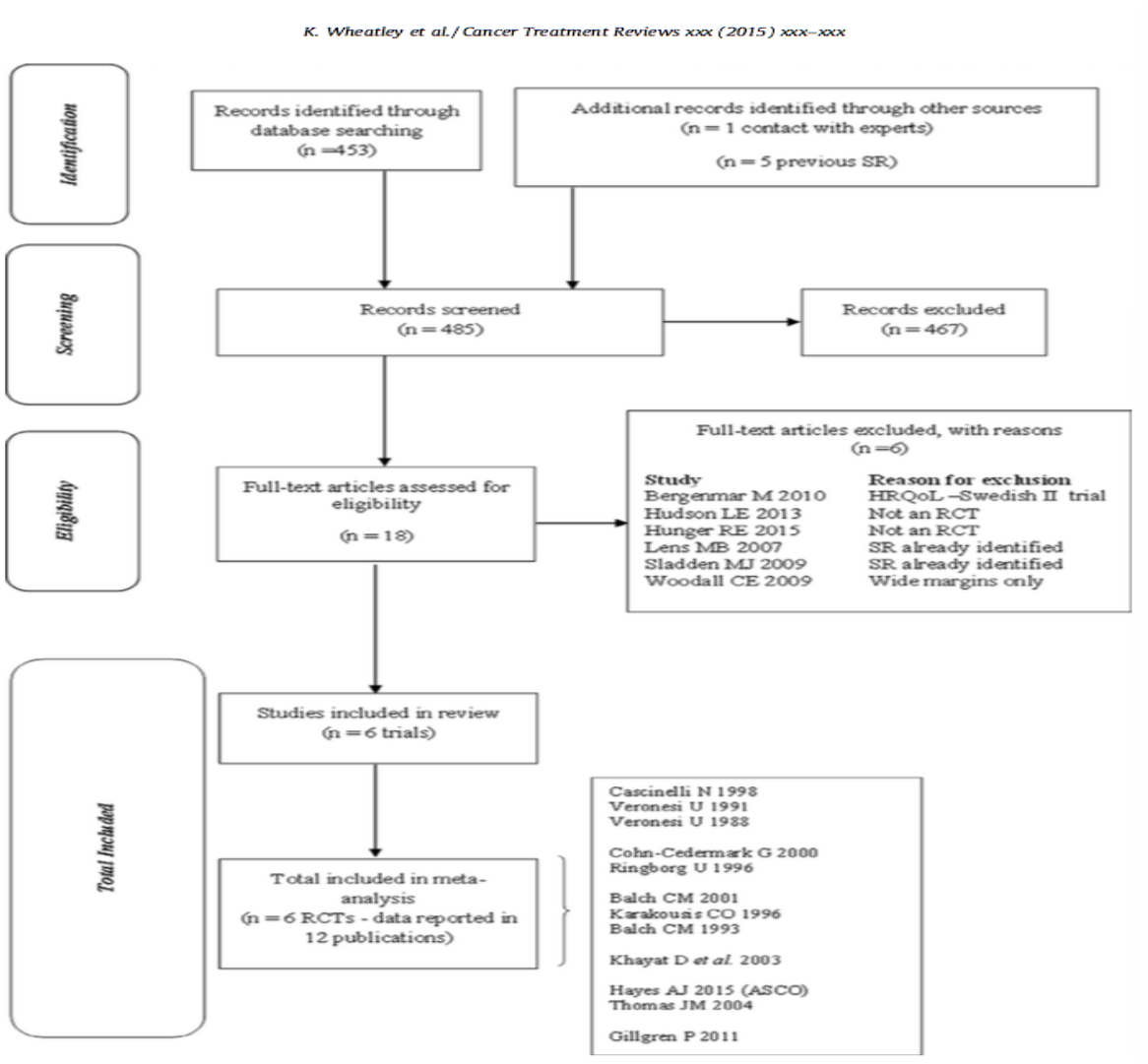

Fig. 1. PRISMA diagram searches published trials 2009 to August 2015.

The margins compared were: 1 cm versus 3 cm [15,16]; 2 cm versus 4 cm [17,18]; 2 cm versus 5cm [19,20]. Three trials consisted of patients with tumors 62.0 mm thick [5,6,20]; two included patients with growths > 2.0 mm thick [16,18]; one consisted of patients with tumors in between 1.0 and 4.0 mm thick [7] although the results split by 62.0 mm and > 2.0 mm were reported. Data on loco-regional re-occurrence and recurrence-free survival were reported for all six trials; data on general survival might have been reported for all 6 trials, though there is some unpredictability concerning the Intergroup trial [7,21](see Discussion); melanoma-specific survival was reported in four trials [6,7,9,12]. The qualities of all trials are reported in Table 2.

Trial name associated publications	No. Pts. narrow/wide	General characteris-tics	Breslow thickness	Resection margin narrow	Resection margin wide	Difference in margin width	Outcomes reported
WHO melanoma trial Cascinelli et al. (1998)[25] Veronesi et al. (1991)[26] Veronesi et al (1988)[27]	305/307	Stage I primary cutaneous melanoma	62 mm	1 cm	3 cm	2 cm	OS, MSS, RFS, LRR
Swedish I Cohn-Cedermark et al. (2000)[28] Ringborg et al. (1996)[29]	476/513	Primary cutaneous, melanoma measuring.>0.8 mm and 62.0 mm in thickness with a trunk or extremity location (except hands and feet)	>0.8 mm And 62.0 mm	2 cm	5 cm	3 cm	OS, MSS, RFS, LRR
Intergroup melanoma trial Balch et al. (2001)[30] Karakousis et al. (1996)[31] Balch et al. (1993)[32]	244/242	Primary melanoma stages I, II occurring on the trunk and above knee and elbow	1–4 mm	2 cm Including muscle fascia	4 cm Including muscle fasci	2 cm	OS, MSS, RFS, LRR
European/French trial Khayat et al. (2003)[33]	161/165	Primary melanoma (except toes, nail or finger or acral-lentiginous melanoma)	62 mm	2 cm	5 cm	3 cm	OS, RFS, LRR
UK Trial BAPS/MSG Thomas et al. (2004)[34] Hayes et al. (2015)[35]	453/447	Primary cutaneous melanoma 2 mm or more, on trunk or limbs where a 3 cm excision margin was possible (except palms of hands or soles of	P2 mm	1 cm	3 cm	2 cm	OS, MSS, RFS, LRR
Swedish II Gillgren et al. (2011) [36]	465/471	Primary cutaneous melanoma thicker than 2 mm and clinically localized to the trunk, upper or lower extremities .	P2 mm	2 cm	4 cm	2 cm	OS, MSS,RFS, LRR

In addition to the finished trials, one continuous trial called the MelMarT Melanoma Margins Trial, NCT01457157 (formerly signed up as NCT02385214) was recognized [22]. This trial compares 1 cm margins with 2 cm margins, both which would be classed as narrow margins in this evaluation. The trial started in 2014 and at first aims to recruit 400 patients for feasibility. If continued, it is anticipated to finish in 2029.

Risk bias of included studies:

For all six RCTs, research study quality was usually good, with much better reporting in the most recent publications The Intergroup [7] and European/French [20] trials cannot explain their randomisation treatments and it was uncertain whether allocation was concealed. 3 trials (Swedish I [6], European [20], Swedish II [12]) reported that patients who had a 2 cm margin excision at their preliminary biopsy did not have even more surgery if allocated a 2 cm margin. This implies that some patients in the narrow group may have had surgery 4-8 weeks prior to patients in the broad group and also that they might 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 readied in all trials. Only the Intergroup trial [17] reported blinding of outcome assessors. A funnel plot for general survival (disappointed) showed small asymmetry with little trials missing in favor of narrow margins. We would assume had these been offered that the trials would have been reported as they would be considered beneficial. It is worth noting that Cochrane recommends a minimum of 10 trials to produce a trusted funnel plot [23].

Overall survival:

The threat ratio for total survival (6 trials) was 1.09 (95% CI 0.98-- 1.22; p = 0.1), with no proof of heterogeneity between the trials (test for heterogeneity: p = 0.7). If the Intergroup trial [24] is left out (see Discussion), the outcomes are: HR 1.07 (95% CI 0.96-1.20; p = 0.2, test for heterogeneity: p = 0.9).

The results of this organized review and quantitative meta- analysis concern the extensive belief that narrow surgical excision margins for primary cutaneous melanoma are therapeutically comparable to wide margins and are safe and for that reason appropriate. This review offers more dependable evidence than previous evaluations because it consists of an extra trial [18] with over 900 patients, adding about 25% more patients to the analysis and an upgrade of the UK trial [13]. The inclusion of these recent data does not essentially alter the outcomes compared to those acquired from the five previously reported trials; for instance, for total survival the threat ratio modifications from 1.07 (95% CI 0.93-- 1.24) to 1.09 (95% CI 0.98-1.22). This review has also, for the first time, examined whether there is any proof of different treatment results in two subgroups; one by the randomized concern and one by the Breslow density of the growth. We discovered no evidence that the treatment impact in trials of 1 cm versus 3 cm margins varied from that observed in trials of 2 cm versus 4 or 5 cm margins or that it varied in patients with better diagnosis tumors <2 mm thick compared with those with thicker tumors. Our analyses suggest that there may be a 94% probability that overall survival is even worse with using a narrow, or 1-2 cm margin, and a 43% probability that it is more than 10% even worse in proportional terms; these values end up being 88% and 31% respectively if the Intergroup trial [24] is left out

4. CONCLUSION

In conclusion, there is no clear evidence that narrow 1-2 cm surgical margins are safe when compared with wide 3-5 cm margins for the treatment of primary cutaneous melanoma. Certainly, there is some evidence that they might be hazardous. There is statistically considerably worse melanoma-specific survival with narrow margins and a high possibility for all endpoints on possibility analysis that a narrow margin is worse. More proof is needed. A more big trial is ongoing comparing 1 cm versus 2 cm margins, but without a wider margin arm [22]. This style is arguable offered the present state of knowledge, and the omission of a 3 cm or broader margin arm is an oversight. Any future trial will take several years to report and conduct. In the meantime, this unpredictability needs to inform surgical choices about which margin width to use and the benefits and drawbacks of the margin width options should be fully gone over with patients.

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