

Melanoma: assessment and management

[C] Evidence review for surgical and histological excision margins for people with stage 0 to II melanoma

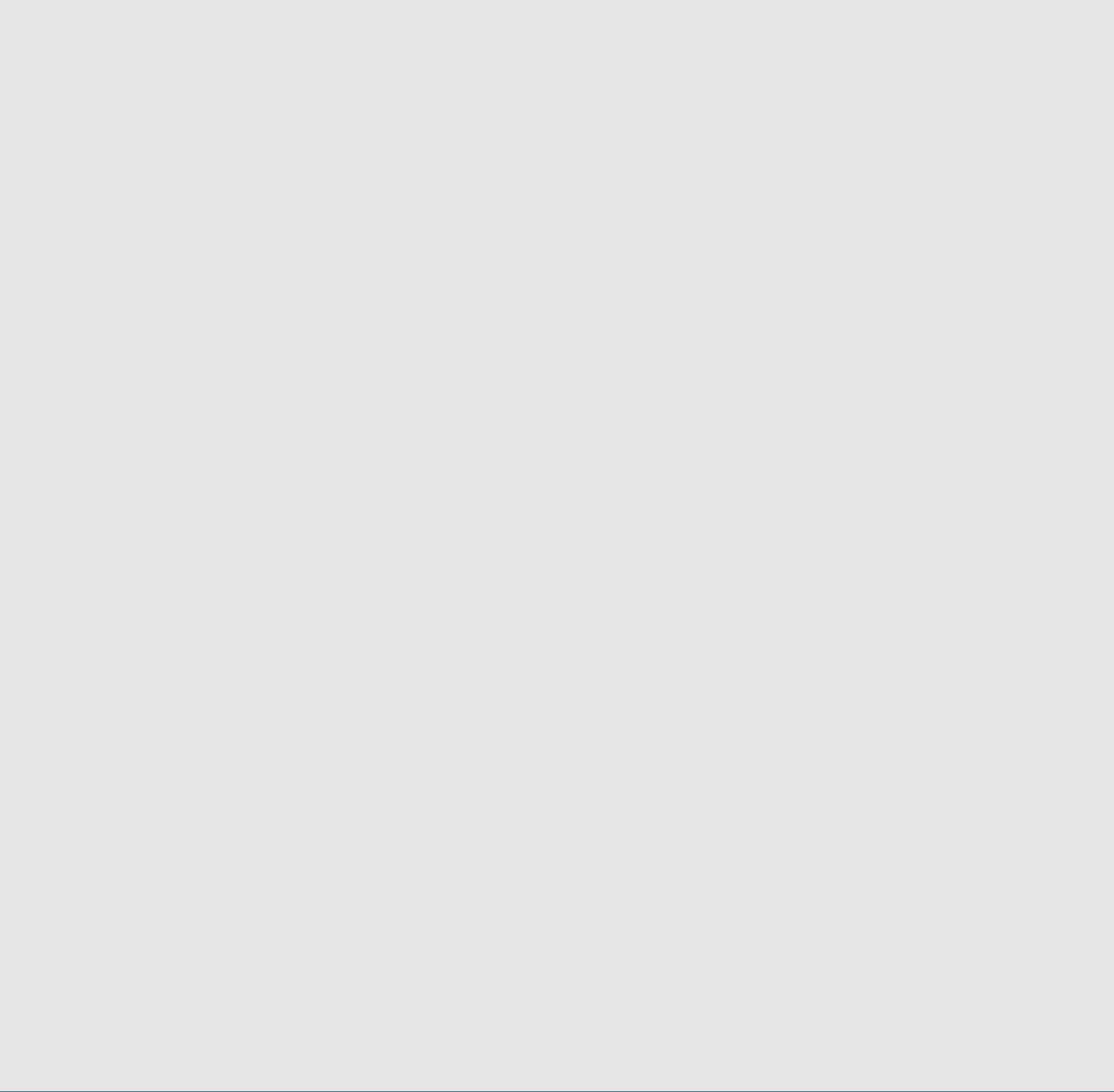
NICE guideline NG14

Evidence reviews underpinning recommendations 1.5.1 to 1.5.3 and research recommendations in the NICE guideline

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Final

*These evidence reviews were developed
by Guideline Updates Team*



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Surgical and histological excision margins for people with stage 0 to II melanoma

1.1 Review question

What are the most effective surgical and histological excision margins for stage 0 to II melanoma?

1.1.1 Introduction

There is a lack of consensus regarding optimal surgical excision margins for primary cutaneous melanoma. Guidelines for surgical margins of resection vary internationally, from 1 to 3 cm (which may lead to excision defects from 2 to 6 cm in diameter). There is a growing concern internationally amongst surgeons that the excess morbidity caused by larger excision defects may not be necessary.

Input from stakeholders during draft scope consultation and committee topic experts highlighted there was a need to update recommendations on the size of excision margins used to treat stage 0-2C melanoma. In particular, it is unclear when an excision margin of 3cm has clinical benefit compared to smaller margins for people with stage 1A-2C melanoma.

1.1.2 Summary of the protocol

Table 1 PICO table for surgical and histological excision margins for stage 0 to 2 melanoma

Population	People with a diagnostic of stage 1a-2C melanoma
Intervention (predictors)	Stage 1A – 2C melanoma: Excision margin <ul style="list-style-type: none"> • ≤1cm • 1-2cm • 2-3cm
Comparator (predicted outcome)	Compared to each other
Outcomes	<ul style="list-style-type: none"> • Pathological clear margins • Local Recurrence • Regional recurrence • All-cause and Melanoma-related mortality (5 & 10 yr) • HRQL • Detection of micro metastases • Adverse events, inc: Cosmesis & surgical reconstruction

1.1.3 Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual](#). Methods specific to this review question are described in the review protocol in appendix A and [Developing NICE guidelines: the manual](#).

Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

Protocol deviation

The protocol specified looking at excisional margins between 1 and 3cm. However, the committee agreed that it was also useful to look at wider excisional margins so long as they were compared against a margin between 1 and 3cm. The protocol was expanded to account for this.

1.1.4 Clinical evidence

1.1.4.1 Included studies

A systematic literature search was conducted for this review on systemic and localised treatment in people with melanoma. This returned 1,581 references (see appendix B for the literature search strategy). Based on title and abstract screening against the review protocol, 48 references were ordered for screening based on their full texts.

Of the 48 references screened as full texts, 17 references (representing 8 distinct trials) met the inclusion criteria specified in the review protocol for this question (appendix A). The clinical evidence study selection is presented as a diagram in appendix C.

1.1.4.2 Excluded studies

See Appendix J for a list of references for excluded studies, with reasons for exclusion.

1.1.5 Summary of studies included in the clinical evidence

Table 2 Summary of included studies

Study	Sample size	Inclusion criteria	Interventions	Follow-up time	Risk of bias (notes)
MelMarT trial	400	Diagnosis (by shave or excision biopsy) of a primary cutaneous melanoma of Breslow thickness 1 mm	1cm vs 2cm excision	Up to 12 months	Moderate <i>Outcome assessment was unblinded. Unclear how analysis was undertaken (e.g. per protocol or ITT), participants were excluded for ineligibility but details not provided.)</i>
UK - MSG	900	Single, primary, localized cutaneous melanoma 2 mm or greater in thickness on the trunk or limbs (excluding the palms of the hands or the soles of the feet), where a 3-cm excision margin was possible.	1cm vs 3 cm excision	Median follow-up of 8.8 years	Moderate <i>Open-label</i> <i>There were protocol deviations in 14.0 percent of the patients; the majority were minor. Some alteration of end points (protocol deviation)</i>
WHO melanoma group	612	All patients had cutaneous melanoma with \leq 2 mm thickness on trunk or limbs (not fingers, toes, face)	1cm vs \geq 3 cm	5 years (mean duration of follow up was 55 months in both arms) and 12 year follow up in a later study	High <i>A significant number of participants were excluded following randomisation (75/612 = 12%). While the majority of these were due to non-eligibility discovered following randomisation, 15 were due to a "mistake in treatment" and 1 due to "loss to follow up". This suggests a per protocol approach to analysis. In addition, neither participants nor assessors were blinded.</i>

Study	Sample size	Inclusion criteria	Interventions	Follow-up time	Risk of bias (notes)
Intergroup Melanoma Surgical Trial	470	All patients had cutaneous melanoma of 1-4 mm thickness on trunk or limbs, with no evidence of metastatic melanoma in lymph nodes or distant sites	2cm vs 4cm excision	Median 10 year follow up	Moderate <i>The studies lacked detail about any protocol deviations or missing data. In addition, some outcomes were altered in one paper, but with justification.</i>
SMSG - DMG	936	Diagnosed with localised cutaneous melanoma thicker than 2 mm, and with primary site on the trunk or upper or lower extremities	2cm vs 4cm excision	Median follow-up of 6-7 years	Moderate <i>Lack of blinding at any point and some minor protocol deviations, as well as a greater proportion of patients in the 2cm group undergoing sentinel node biopsy, however these were unlikely to impact the results of the trial.)</i>
Bergenmar 2010	165	A histologically-confirmed diagnosis of cutaneous malignant melanoma more than 2.00 mm thick (T3–T4), situated on the trunk or extremities (except hands and feet).	2cm vs 4cm excision	Up to 15 months	High <i>The first assessment was done before randomisation. Unclear how randomisation was performed. Unclear if allocation concealment. Very few baseline characteristics were reported with which to assess the success of randomisation. Unclear if any deviations from intended intervention. By the end of follow up the amount of missing data was significant (88%). It is unclear how the extent of missing data varied between arms. Insufficient justification or detail for methods provided and protocol is not cited.</i>
SMSG	989	All patients had cutaneous melanoma with > 0.8 mm ≤ 2 mm thickness on trunk or extremity (not fingers, feet, face).	2cm vs ≥5cm excision	11 years overall survival), 8 years	Moderate

Study	Sample size	Inclusion criteria	Interventions	Follow-up time	Risk of bias (notes)
			The median resection margin in the narrow excision group was 2 cm (range, 0.2–5.5 cm), and it was 5 cm (range, 0.2–10.0 cm) in the wide excision group (mean resection margin, 2.1 cm vs. 4.6 cm).	(recurrence-free survival).	<i>Seventy-five percent of the patients in each treatment group were treated with the exact allocated excision margin. However, it is unclear whether deviations from the intended interventions was as a result of the experimental context. Intention to treat analysis was used. Deviations appeared to be balanced between groups. outcome assessors were unblinded, and for some outcomes e.g. local recurrence, regional cutaneous metastasis, and regional lymph node metastasis, it was unclear which definitions were used.</i>
Large European Multicentric Phase III Study (French Study)	337	All patients had melanoma with ≤ 2 mm thickness on trunk, limbs, head and neck (not fingers, toes, nails); TNM stage 1;	2cm vs ≥ 5 cm excision	16 years	High <i>Non-blinded assessments. Unclear approach to analysis (e.g. intention to treat). Unclear approach to randomisation or allocation concealment. Large attrition/ missing data at 20 years follow up</i>

See appendix D for full evidence tables.

1.1.6 Summary of clinical evidence

Table 3 Summary of included studies

Study	Sample size	Intervention(s)	GRADE quality	Summary of findings (significant findings are highlighted in bold)
MelMarT	400	1cm vs 2cm excision	Low	Quality of life at 12 months post-randomisation measured using the FACT-M questionnaire (version 4) (HR<1 favours narrow excision margin): “there was no difference in quality of life or neuropathic pain data in any domain between the 1 and 2-cm groups. Similarly, there were no differences between the two margins in any subgroup analyses.”
			Moderate	Reconstruction surgery at 12 months post-randomisation (OR<1 favours narrow excision margin): OR 0.29 [0.18, 0.49]
			Very Low	Total surgical adverse events including: wound dehiscence; haematoma; haemorrhage; wound infection; or wound necrosis post-intervention (OR<1 favours narrow excision margin): OR 0.89 [0.46, 1.70]
			Very Low	Wound dehiscence post intervention (OR<1 favours narrow excision margin): OR 1.04 [0.26, 4.24]
			Very Low	Haematoma (Grade I or IIIa) post intervention (OR<1 favours narrow excision margin): OR 1.57 [0.26, 9.53]
			Very Low	Haemorrhage post intervention (OR<1 favours narrow excision margin): No participants experienced haemorrhage (effect size not estimable)
			Very Low	Wound infection (Grade I or II) post intervention (OR<1 favours narrow excision margin): OR 1.29 [0.52, 3.20]
			Low	Wound necrosis (including partial/total loss of skin graft) post intervention (OR<1 favours narrow excision margin): OR 0.14 [0.02, 1.19]
UK-MSG	900	1cm vs 3cm excision	Moderate	Deaths due to any cause (follow up was 68 months [IQR 35–103]) (HR<1 favours narrow excision margin): HR 1.14 [95% CI 0.96–1.36]
			Moderate	Deaths due to any cause (median follow up 60 months – HR<1 favours narrow excision margin): HR 1.07 (0.85–1.36)
			Moderate	Melanoma-specific deaths over follow up (follow up was 68 months [IQR 35–103]) (HR<1 favours narrow excision margin): HR 1.24 [95% CI 1.01–1.53]
			Moderate	Melanoma-specific deaths (median follow up 60 months – HR<1 favours narrow excision margin): HR 1.24 (0.96–1.61)
			Moderate	Overall Survival over follow up (follow up was 68 months [IQR 35–103]) (HR<1 favours narrow excision margin): HR 1.19 (0.99–1.45)
			Moderate	Melanoma-specific survival over follow up (follow up was 68 months [IQR 35–103]) (HR<1 favours narrow excision margin): aHR 1.28 (1.02–1.61)
			Moderate	Locoregional recurrence (median follow up 60 months – HR<1 favours narrow excision margin): Local recurrence was defined as a recurrence within 2 cm of the scar or

Study	Sample size	Intervention(s)	GRADE quality	Summary of findings (significant findings are highlighted in bold)
				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: HR 1.26 (1.00 to 1.59)
			Moderate	Recurrence or death (median follow up 60 months – HR<1 favours narrow excision margin): defined as above: HR 1.21 (0.99 to 1.46)
			Moderate	Local or in-transit recurrence (median follow up 60 months – HR<1 favours narrow excision margin): defined as above: HR 1.51 (0.91 to 2.51)
			Moderate	Regional -node recurrence (median follow up 60 months – HR<1 favours narrow excision margin): defined as above: HR 1.21 (0.96–1.53)
	426		Moderate	“Poor” vocational adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined: OR 1.66 (0.68 to 4.08)
	Moderate		“Poor” domestic adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined: OR 3.11 (1.17–8.27)	
	Moderate		“Poor” sexual adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined: OR 1.92 (0.70–5.31)	
	Moderate		“Poor” extended family adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined: OR 1.09 (0.43–2.75)	
	Moderate		“Poor” social adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined: OR 4.22 (1.54–11.55)	
	392		Moderate	Physical component summary score (maximum follow up time = 2 years; coefficient<0 favours narrow excision margin): measured using the Medical Outcomes Survey–Short Form (MOS-SF36): Coefficient= – 157.0, SE= 83.5, p=0.06
	Moderate		Mental component summary score (maximum follow up time = 2 years; coefficient<0 favours narrow excision margin): measured using the Medical Outcomes Survey–Short Form (MOS-SF36): Coefficient= – 133.1, SE= 91.6, p=0.151	
	900		High	Total surgical complications: not defined - OR 0.49 [0.32, 0.76]

Study	Sample size	Intervention(s)	GRADE quality	Summary of findings (significant findings are highlighted in bold)
	128		Very Low	Partial or complete graft loss post intervention (OR<1 favours narrow excision margin): OR 0.48 [0.22, 1.04]
			Very Low	Wound dehiscence post intervention (OR<1 favours narrow excision margin): OR 0.76 [0.28, 2.07]
			Moderate	Perception of scar (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the last Cassileth Scar score on follow up: OR 5.55 (2.06–14.98)
WHO	612	1cm vs ≥3cm excision	Very Low	Recurrence-free survival at a median follow-up of 55 months (OR>1 favours narrow excision margin): OR 1.12 [0.64, 1.95]
			Very Low	Recurrence-free survival over 8-years follow up (OR>1 favours narrow excision margin): OR 0.82 [0.54, 1.26]
			Very Low	Local recurrence at a mean follow up of 55 months (OR<1 favours narrow excision margin): OR 7.12 [0.37, 138.34]
			Very Low	Local recurrence (first recurrence) at 8 years (OR<1 favours narrow excision margin): OR 9.18 [0.49, 171.23]
			Very Low	In-transit metastases at a mean follow up of 55 months (OR<1 favours narrow excision margin): OR 2.02 [0.18, 22.39]
			Very Low	In-transit metastases (first recurrence) at 8 years follow up (OR<1 favours narrow excision margin): OR 1.01 [0.14, 7.19]
			Very Low	Regional nodal metastases at a mean follow up of 55 months (OR<1 favours narrow excision margin): OR 0.69 [0.34, 1.39]
			Very Low	Regional nodal metastases (first recurrence) at 8 years follow up (OR<1 favours narrow excision margin): OR 0.87 [0.47, 1.60]
			Very Low	Distant metastases at a mean follow up of 55 months (OR<1 favours narrow excision margin): OR 0.88 [0.31, 2.45]
			Very Low	Distant metastases (first recurrence) at 8 years follow up (OR<1 favours narrow excision margin): OR 1.24 [0.60, 2.55]
			Very Low	Any recurrence at a mean follow up of 55 months (OR<1 favours narrow excision margin): OR 0.89 [0.51, 1.56]
			Very Low	Any recurrence at 8 years follow up (OR<1 favours narrow excision margin): OR 1.13 [0.71, 1.78]
			Very Low	Overall survival at a median follow-up of 55 months (OR>1 favours narrow excision margin): OR 1.20 [0.51, 2.82]
			Very Low	Overall survival at 8 years (OR>1 favours narrow excision margin): OR 0.92 [0.55, 1.56]
Very Low	Overall survival at 12 years (OR>1 favours narrow excision margin): OR 1.20 [0.76, 1.90]			
Very Low	Recurrence-free survival at a median follow-up of 55 months (OR>1 favours narrow excision margin): OR 1.12 [0.64, 1.95]			

Study	Sample size	Intervention(s)	GRADE quality	Summary of findings (significant findings are highlighted in bold)
Intergroup Melanoma Surgical Trial	468	2cm vs 4cm excision	Very Low	Local recurrence as a first recurrence with a median follow-up of 10 years and a range up to 16 years (OR<1 favours narrow excision margin): OR 0.48 [0.04, 5.34]
			Very Low	Local recurrence at any time with a median follow-up of 10 years and a range up to 16 years (OR<1 favours narrow excision margin): OR 0.80 [0.24, 2.66]
			Very Low	Local recurrence after a median follow up time of 92 months (OR<1 favours narrow excision margin): OR 0.81 [0.24, 2.69]
			Very Low	Local recurrence after a median follow up time of 72 months (OR<1 favours narrow excision margin): OR 0.33 [0.06, 1.63]
			Very Low	In-transit metastases after a median follow up time of 72 months (OR<1 favours narrow excision margin): OR 1.19 [0.36, 3.97]
			Very Low	In-transit metastases after a median follow up time of 72 months (OR<1 favours narrow excision margin): OR 1.31 [0.72, 2.39]
			Low	Overall disease-free survival at 5 years (OR>1 favours narrow excision margin): OR 0.75 [0.48, 1.16]
			Low	Overall survival at a median follow-up of 10 years (OR>1 favours narrow excision margin): OR 0.70 [0.47, 1.07]
			Low	Overall survival at 5 years (OR>1 favours narrow excision margin): OR 0.75 [0.47, 1.18]
			Moderate	Need for a skin graft following intervention (OR<1 favours narrow excision group): OR 0.20 [0.10, 0.40]
			Low	Length of hospital stay following intervention (MD<0 favours narrow excision group): MD -1.80 [-2.66, -0.94]
			Very Low	Wound infection rate following intervention (OR<1 favours narrow excision group): OR 1.18 [0.52, 2.69]
Very Low	Wound dehiscence rates following intervention (OR<1 favours narrow excision group): OR 1.10 [0.46, 2.63]			
SMSG - DMG	936	2cm vs 4cm excision	Low	Local recurrence over follow up (median 6.7 years) (HR<1 favours narrow excision margin): HR 2.15 (0.97–4.77)
			Very Low	Regional skin metastases over follow up (median 6.7 years) (HR<1 favours narrow excision margin): HR 1.25 (0.63–2.46)
			Low	Regional lymph node recurrence over follow up (median 6.7 years) (HR<1 favours narrow excision margin): HR 0.88 (0.68–1.16)
			Very Low	Any local recurrence over follow up (median 6.7 years) (HR<1 favours narrow excision margin): HR 1.00 (0.79–1.28)
			Low	Distant metastasis over follow up (median 6.7 years) (HR<1 favours narrow excision margin): HR 0.71 (0.47–1.08)
			Low	Overall survival at a median follow-up of 6.7 years (HR>1 favours narrow excision margin): HR 1.11 (0.90–1.37)

Study	Sample size	Intervention(s)	GRADE quality	Summary of findings (significant findings are highlighted in bold)
			Moderate	Overall disease-free survival at 6.7 years (HR>1 favours narrow excision margin): HR 1.01 (0.83–1.24)
			Moderate	Rate of death over follow up (median 19.6 years) (HR<1 favours narrow excision margin): HR 0.98 (0.83–1.14)
			Low	Melanoma-specific rate of death over follow up (median 19.6 years) (HR<1 favours narrow excision margin): HR 0.95 (0.78–1.16)
			Moderate	Rate of death over follow up (median 19.6 years) (HR<1 favours narrow excision margin): HR 1.02 (0.87–1.19)
			Moderate	Melanoma-specific rate of death over follow up (median 19.6 years) (HR<1 favours narrow excision margin): HR 0.99 (0.81–1.20)
			Low	Rate of death over follow up (median 6.7 years) (HR<1 favours narrow excision margin): HR 1.05 (0.85–1.29)
			Very Low	Melanoma-specific rate of death over follow up (median 6.7 years) (HR<1 favours narrow excision margin): HR 0.99 (0.78–1.26)
			Moderate	Need for a skin graft following intervention (OR<1 favours narrow excision group): OR 0.16 [0.11, 0.22]
Bergenmar 2010 (?Swedish Melanoma Group)	144	2cm vs 4cm excision	Very Low	“Problems with the scar” at 4 or 15 months following randomisation (OR<1 favours narrow excision group): OR 0.64 [0.28, 1.46]
			Very Low	Physical functioning score at 3 months post-randomisation, measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) (higher score = better functioning): MD 1.63 [-1.53, 4.79]
			Very Low	Physical functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD -1.35 [-4.80, 2.10]
			Low	Role functioning score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 3.29 [-5.00, 11.58]
			Very Low	Role functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD -2.49 [-7.09, 2.11]
			Low	Emotional functioning score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 3.73 [0.89, 6.57]
			Low	Emotional functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 1.54 [-4.29, 7.37]
			Low	Cognitive functioning score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 2.01 [-2.87, 6.89]
			Low	Cognitive functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 0.18 [-4.58, 4.94]

Study	Sample size	Intervention(s)	GRADE quality	Summary of findings (significant findings are highlighted in bold)
			Very Low	Social functioning score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 3.84 [-1.78, 9.46]
			Very Low	Social functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 3.07 [-1.84, 7.98]
			Very Low	Global quality of life at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 4.87 [-1.81, 11.55]
			Very Low	Global quality of life at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 2.96 [-3.92, 9.84]
			Very Low	Fatigue score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD -6.19 [-12.47, 0.09]
			Low	Fatigue score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD -0.26 [-6.77, 6.25]
			Low	Pain score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD -1.98 [-7.97, 4.01]
			Very Low	Pain score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 2.60 [-3.47, 8.67]
			Very Low	Insomnia score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD -8.34 [-15.91, -0.77]
			Low	Insomnia score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD 2.57 [-5.32, 10.46]
			Low	Financial difficulties score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD -2.49 [-9.23, 4.25]
			Low	Financial difficulties score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning): MD -0.29 [-4.14, 3.56]
			Low	Clinical anxiety score at 3 months post randomisation, measured using the HAD-A questionnaire (higher score = better functioning): MD -0.10 [-1.58, 1.38]
			Very Low	Clinical anxiety score at 15 months post randomisation, measured using the HAD-A questionnaire (higher score = better functioning): MD -0.56 [-2.24, 1.12]
			Very Low	Clinical depression score at 3 months post randomisation, measured using the HAD-D questionnaire (higher score = better functioning): MD -0.36 [-1.38, 0.66]
			Low	Clinical depression score at 15 months post randomisation, measured using the HAD-D questionnaire (higher score = better functioning): MD -0.17 [-1.39, 1.05]

Study	Sample size	Intervention(s)	GRADE quality	Summary of findings (significant findings are highlighted in bold)
Large European Multicentric Phase III Study	326	2cm vs ≥5cm excision	Very Low	No tumour recurrence at 20 years of follow up (OR>1 favours narrow excision group): OR 1.11 [0.72, 1.73]
			Very Low	Disease-free survival at 10 years of follow up (OR>1 favours narrow excision group): OR 1.17 [0.64, 2.11]
			Very Low	Overall survival at 10 years of follow up (OR>1 favours narrow excision group): OR 1.08 [0.57, 2.04]
			Very Low	Tumour recurrence at 20 years of follow up (OR<1 favours narrow excision group): OR 0.63 [0.35, 1.14]
			Very Low	Death at 20 years of follow up (OR<1 favours narrow excision group): OR 1.16 [0.67, 2.03]
			Very Low	Local recurrence at 20 years of follow up (OR<1 favours narrow excision group): OR 0.25 [0.03, 2.28]
			Very Low	Distant recurrence at 20 years of follow up (OR<1 favours narrow excision group): OR 0.39 [0.12, 1.29]
			Very Low	Regional lymph node recurrence at 20 years of follow up (OR<1 favours narrow excision group): OR 1.23 [0.53, 2.83]
SMSG	989	2cm vs ≥5cm excision	Low	Overall survival at a median follow-up of 11 years [range 7 to 17 years] (HR <1 favours narrow excision margin): HR 0.96 (0.75–1.24)
			Very Low	Any death at a median follow-up of 5.8 years (HR <1 favours narrow excision margin): HR 1.00 (0.68-1.47)
			Low	Melanoma-specific survival (from death) over follow up (median 11 years) (HR<1 favours narrow excision margin): HR 1.22 (0.88–1.69)
			Very Low	Melanoma specific death at a median follow-up of 5.8 years (HR <1 favours narrow excision margin): HR 1.31 (0.79-2.15)
			Low	Locoregional recurrence with a median follow-up of 8 years [range 0 to 17 years] (HR<1 favours narrow excision margin) defined as local recurrence, regional skin metastases, or regional lymph node metastases: HR 1.24 (0.88–1.75)
			Very Low	Distant metastases with a median follow-up of 8 years [range 0 to 17 years] (HR<1 favours narrow excision margin): HR 0.76 (0.45–1.28)
			Very Low	New primary melanoma with a median follow-up of 8 years [range 0 to 17 years] (HR<1 favours narrow excision margin): HR 1.42 (0.59–3.40)
			Very Low	Any event with a median follow-up of 8 years [range 0 to 17 years] (HR<1 favours narrow excision margin) defined as locoregional recurrence, distant metastasis, new primary melanoma, or intercurrent death: HR 0.75 (0.43–1.30)
			Very Low	Local recurrence at a median follow up of 4 years (HR<1 favours narrow excision margin): HR 0.87 (0.19-3.91)
			Very Low	Regional cutaneous metastasis at a median follow up of 4 years (HR<1 favours narrow excision margin): HR 1.44 (0.50-4.17)
	769			

Study	Sample size	Intervention(s)	GRADE quality	Summary of findings (significant findings are highlighted in bold)
			Low	Regional lymph node metastasis at a median follow up of 4 years (HR<1 favours narrow excision margin): HR 1.56 (0.99-2.45)
			Very Low	Distant metastases at a median follow up of 4 years (HR<1 favours narrow excision margin): HR 1.22 (0.77-1.93)
			Very Low	Any recurrence at a median follow up of 4 years (HR<1 favours narrow excision margin): HR 1.07 (0.78-1.46)

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 7,545 studies. Based on title and abstract screening, 7,543 of the studies could confidently be excluded for this question. Two studies were excluded following the full-text review. Thus, the review for this question did not include any studies from the existing literature.

1.1.7.2 Excluded studies

See Appendix J for a list of references for excluded studies, with reasons for exclusion.

- 1 **1.1.8 Summary of included economic evidence**
- 2 There are no existing economic studies for this review question.

1.1.9 Economic model

No original modelling was completed for this review question

1.1.10 Unit costs

No unit costs were supplied for this review question.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1 The outcomes that matter most

The committee were influenced more by outcomes with clear clinical definitions and substantial implications for the patient, such as mortality rates and disease recurrence. As described above, these were the most commonly reported outcomes, with good follow-up (up to 5 and 10 years). The committee were also particularly interested in the differences in adverse events occurring across studied surgical methods to provide a balanced view of the personal cost of treatment options, beyond disease control. The most commonly reported adverse events were reconstruction surgery and wound dehiscence (reported in three trials each).

1.1.11.2 The quality of the evidence

The identified trials most commonly reported mortality or survival figures (reported in six trials), loco-regional recurrence (reported in six trials), recurrence-free survival (reported in four trials), distant metastases (reported in four trials), and quality of life (reported in three trials).

Two studies were rated as "low" risk of bias, 3 "Moderate", and 3 "high" risk of bias. The most common reason for marking down study risk of bias was as a result of unblinded outcome assessment (five trials) and as a result of missing information leading to a lack of clarity about study methods (five trials) for example: the approach to analysis (e.g. per protocol or intention-to-treat); allocation concealment; reasons for study exclusions; or lack of obvious protocol or a priori approach. Five studies were marked down for quality for not having a clear description of the outcomes of interest (e.g. clear definitions of nodal recurrence or the staging systems used).

The committee were largely interested in the comparisons between excision margins under 1 cm, 1 – 2 cm, and 2 – 3 cm and the comparisons of these margins to each other. Since surgical approaches had moved-on, and were becoming more exact, they were less interested in some of the older studies comparing 2 cm and 3 cm margins to much wider margins such as 4 and 5 cm. The committee noted that the all the considered evidence were using clinical margins rather than histological margins, this meant that they could not make recommendations on what would constitute adequate histological margins following surgery.

The committee were particularly interested in the quality of evidence arising from one trial (UK MSG) which was pivotal to decision making regarding whether to recommend a narrower excision margin than 2 cm (the current standard in many cases in stage 1A to 2C melanoma). This study compared 1 cm excision margin to 3 cm margins and found that the narrow excision margin was associated with greater melanoma-specific mortality and locoregional recurrence (further discussion below). The trial had excluded the use of sentinel node biopsy. Therefore, the committee could not tell whether the rates of positive sentinel node differed between treatment arms and could be biasing results. The committee discussed this but agreed that randomisation should have helped to account for this possibility and noted that the study arms were well matched for other key prognostic factors such as Breslow thickness and ulceration.

In addition, the committee noted that one of the significant outcomes (locoregional recurrence) was calculated by combining the rates of local or in-transit recurrence with the rate of nodal recurrence into the single primary end point of locoregional recurrence, and that this was a protocol deviation that occurred once the study was underway. However, the trend for melanoma-specific survival was in the same direction, showing a greater number of melanoma-specific deaths in the 1cm arm, albeit non-significant.

1.1.11.3 Benefits and harms

As described above, the committee first considered the results of older studies comparing 2cm excision margins to much wider excision margins such as 4 cm and 5 cm. These studies found no significant difference between groups for survival, disease recurrence, or metastases. However, the committee noted the significantly worsened adverse impacts of the surgery itself on outcomes in patients of the wider excision margin groups. For example, greater need for skin grafts and increased length of stay in hospital. With no evidence of benefit for disease control in the wider margin groups, the committee ruled out the routine use of such wide margins for melanoma.

Next the committee considered the WHO melanoma group trial, which compared 1 cm vs ≥ 3 cm excision margins in those with primary melanoma (≤ 2 mm thickness). This trial found that there was no significant differences between study arms for overall survival or disease recurrence. Following this the committee considered evidence from the UK-MSG trial. Which compared 1 cm margins to 3 cm margins in those with >2 mm thickness. This trial found that the 1 cm margin group was associated with a statistically significant worsened rate of melanoma-specific mortality, as well as worsened loco-regional recurrence defined as a local recurrence within 2 cm of the scar or graft; In-transit recurrence beyond the first 2 cm of the scar or metastases to the regional nodes. Conversely, the wider surgical margin was associated with “poor” domestic and social adjustment to illness scores as well as worsened perception of scar scores. Total surgical complications were also significantly higher in the 3 cm margin group (most common were graft loss and wound dehiscence).

The committee considered evidence from the MelMarT trial which included those with >1 mm thick melanoma and showed that there was no significant difference between those with 1 cm and 2 cm margins for quality of life scores or neuropathic pain, but that the need for reconstruction surgery was significant greater in the 2 cm excision group. Unfortunately, this study was only a pilot trial, with a short follow up (12 months) and no survival or recurrence outcomes. The committee noted that another definitive trial (MelMarT 2) was currently underway to help provide long term follow up and sufficient statistical power to assess the relative effects of this important comparison in excision margins.

The committee noted that narrower margins produce much better results for patients in terms of cosmesis and the need for grafts and reconstructive surgery. There are also instances where a narrower margin of 1 cm is routine regardless of Breslow thickness, for example in the head and neck region (including the eyelid) because of functional and cosmetic constraints. However they felt that there remained considerable uncertainty about the relative effectiveness of the 1 cm margin compared to the current most clinically used 2 cm margin. Especially, there was lacking sufficiently powered evidence considering results stratified by tumour stage, type, and thickness. The uncertainty of the evidence was sufficient that another trial had passed ethics to consider the use of 1 cm margins vs 2 cm margins (see above). The committee agreed that there was currently insufficient evidence to justify a change in the recommendations in this area. The committee agreed not to make research recommendations regarding clinical margins due to ongoing trials existing in this area. The committee did make a research recommendation aiming to identify optimal histological margins – the amount of normal tissue surrounding a tumour - following surgery.

1.1.11.4 Cost effectiveness and resource use

No published economic evidence was identified from the systematic review. On the basis of clinical evidence presented, the committee elected to retain the surgical and histological excision margins that are currently recommended, given the uncertainty in the evidence for the use of alternative margins such as for those < 2 cm, which would also lead to uncertainty in estimates of cost-effectiveness. Therefore, there were no resource use considerations made by the committee.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 to 1.5.3 and the research recommendation on histological margins.

1.1.13 References – included studies

1.1.13.1 Clinical evidence

Balch, Charles M., et al. "Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial." *Annals of surgery* 218.3 (1993): 262

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Moncrieff MD, Gyorki D, Saw R, Spillane AJ, Peach H, Oudit D, Geh J, Dziewulski P, Wilson E, Matteucci P, Pritchard-Jones R. 1 versus 2-cm excision margins for pT2-pT4 primary cutaneous melanoma (MelMarT): a feasibility study. *Annals of surgical oncology*. 2018 Sep;25(9):2541-9.

Newton-Bishop JA, Nolan C, Turner F, McCabe M, Barrett JH, Boxer C, Thomas JM, Coombes G, A'Hern RP. A quality-of-life study in high-risk (thickness \geq 2 mm) cutaneous melanoma patients in a randomized trial of 1-cm versus 3-cm surgical excision margins. *InJournal of Investigative Dermatology Symposium Proceedings 2004 Mar 1 (Vol. 9, No. 2, pp. 152-159)*. Elsevier.

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Thomas JM, Newton-Bishop J, A'Hern R, Coombes G, Timmons M, Evans J, Cook M, Theaker J, Fallowfield M, O'Neill T, Ruka W. Excision margins in high-risk malignant melanoma. *New England Journal of Medicine*. 2004 Feb 19;350(8):757-66.

Utjés D, Malmstedt J, Teras J, Drzewiecki K, Gullestad HP, Ingvar C, Eriksson H, Gillgren P. 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: long-term follow-up of a multicentre, randomised trial. *The Lancet*. 2019 Aug 10;394(10197):471-7.

Veronesi U, Cascinelli N, Adamus J, Balch C, Bandiera D, Barchuk A, Bufalino R, Craig P, De Marsillac J, Durand JC, Van Geel AN. Thin stage I primary cutaneous malignant melanoma. *New England Journal of Medicine*. 1988 May 5;318(18):1159-62.

Veronesi U, Cascinelli N. (1991) Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. *Archives of surgery*; 26:438–41.

Appendices

Appendix A – Review protocols

Review protocol for surgical and histological excision margins for stage 0 to 2 melanoma

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Surgical and histological excision margins for stage 0 to 2 melanoma
2.	Review question	RQ 3.1 What are the most effective surgical and histological excision margins for stage 0 to 2 melanoma?
3.	Objective	Determine the most effective clinical excision margins for stage 0-2 melanoma
4.	Searches	<p>The following databases will be searched:</p> <ul style="list-style-type: none"> • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE <p>Searches will be restricted by:</p> <ul style="list-style-type: none"> • Date (of last update, 2015)

		<p>The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.</p> <p>The full search strategies for MEDLINE database will be published in the final review.</p>
5.	Condition or domain being studied	Stage 1A-2C melanoma
6.	Population	People with a diagnostic of stage 1a-2C melanoma
7.	Intervention/Test	<p>Excision margin</p> <ul style="list-style-type: none"> • ≤1cm • 1-2cm • 2-3cm
8.	Comparator/Reference standard	Compared to each other
9.	Types of study to be included	<ul style="list-style-type: none"> • RCTs • Prospective cohort studies if no RCTs are found
10.	Other exclusion criteria	None
11.	Context	This review is part of an update of the NICE guideline on melanoma: assessment and management (NG14, 2105). This guideline covers adults and children with melanoma. Input from stakeholders during draft scope consultation and committee topic experts highlighted there was a need to update

		recommendations on the size of excision margins used to treat stage 0-2C melanoma. In particular, it is unclear when an excision margin of 3cm has clinical benefit compared to smaller margins for people with stage 1A-2C melanoma
12.	Primary outcomes (critical outcomes)	<ul style="list-style-type: none"> ● Pathological clear margins ● Local Recurrence ● Regional recurrence ● All-cause and Melanoma-related mortality (5 & 10 yr) ● HRQL ● Detection of micro metastases ● Adverse events, inc: Cosmesis & surgical reconstruction
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		<p>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).</p> <p>Study investigators may be contacted for missing data where time and resources allow.</p> <p>Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.</p>
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane risk of bias tool (version 2), as described in Developing NICE guidelines: the manual .
16.	Strategy for data synthesis	<p>Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).</p> <p>Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met:</p>

		<ul style="list-style-type: none"> • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$
17.	Analysis of sub-groups	<p>Subgroups (to be investigated irrespective of presence of statistical heterogeneity):</p> <ul style="list-style-type: none"> • Pregnant women • Preliminary melanoma stage. • People with a compromised immune system. • Children/adolescents
18.	Type and method of review	<input checked="" type="checkbox"/> intervention
		<input type="checkbox"/>
		<input type="checkbox"/>
		<input type="checkbox"/>
		<input type="checkbox"/>
		<input type="checkbox"/>
		<input type="checkbox"/>
19.	Language	English

20.	Country	England
21.	Anticipated or actual start date	01/03/21
22.	Anticipated completion date	01/09/2021
23.	Stage of review at time of this submission	Review stage
		Preliminary searches
		Piloting of the study selection process
		Formal screening of search results against eligibility criteria
		Data extraction
		Risk of bias (quality) assessment
		Data analysis
24.	Named contact	<p>a. Named contact Guideline updates team</p> <p>b Named contact e-mail skincancer@nice.nhs.uk</p> <p>c Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)</p>

25.	Review team members	<p>From the Guideline Updates Team</p> <ul style="list-style-type: none"> ● Caroline Mulvihill ● Thomas Jarratt ● Brett Doble ● Steph Armstrong ● Hannah Lomax ● Jenny Craven
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.
27.	Conflicts of interest	<p>All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.</p>
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of

		Developing NICE guidelines: the manual . Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10155
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	<ul style="list-style-type: none"> • Excision margin • Histological margin • Melanoma • Skin cancer • Skin tumour

33.	Details of existing review of same topic by same authors	Update of question 5.1 in NICE Guideline NG14 Melanoma: assessment and management
34.	Current review status	<input checked="" type="checkbox"/> completed
35..	Additional information	none
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Topic/question details: Melanoma

RQ 3.1 – Excision margins

What are the most effective surgical and histological excision margins for stage 0 to 2 melanoma?

In Ovid: Date limit of 2015 – current applied to all databases (except Epub Ahead of Print)

McMaster Balanced RCT Filter applied to Ovid searches.

Databases searched

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	07/04/2021	07/04/2021 17:13:04	1101
Cochrane Database of Systematic Reviews (CDSR)	07/04/2021	07/04/2021 17:13:04	32
Database of Abstracts of Reviews of Effect (DARE)	07/04/2021	07/04/2021	1
	07/04/2021	07/04/2021	11

HTA			
Embase (Ovid)	07/04/2021	<1974 to 2021 April 06>	618
MEDLINE (Ovid)	07/04/2021	<1946 to April 06, 2021>	385
MEDLINE In-Process (Ovid)	07/04/2021	1946 to March 24, 2021	37
MEDLINE Epub Ahead of Print^a	07/04/2021	<April 06, 2021>	16

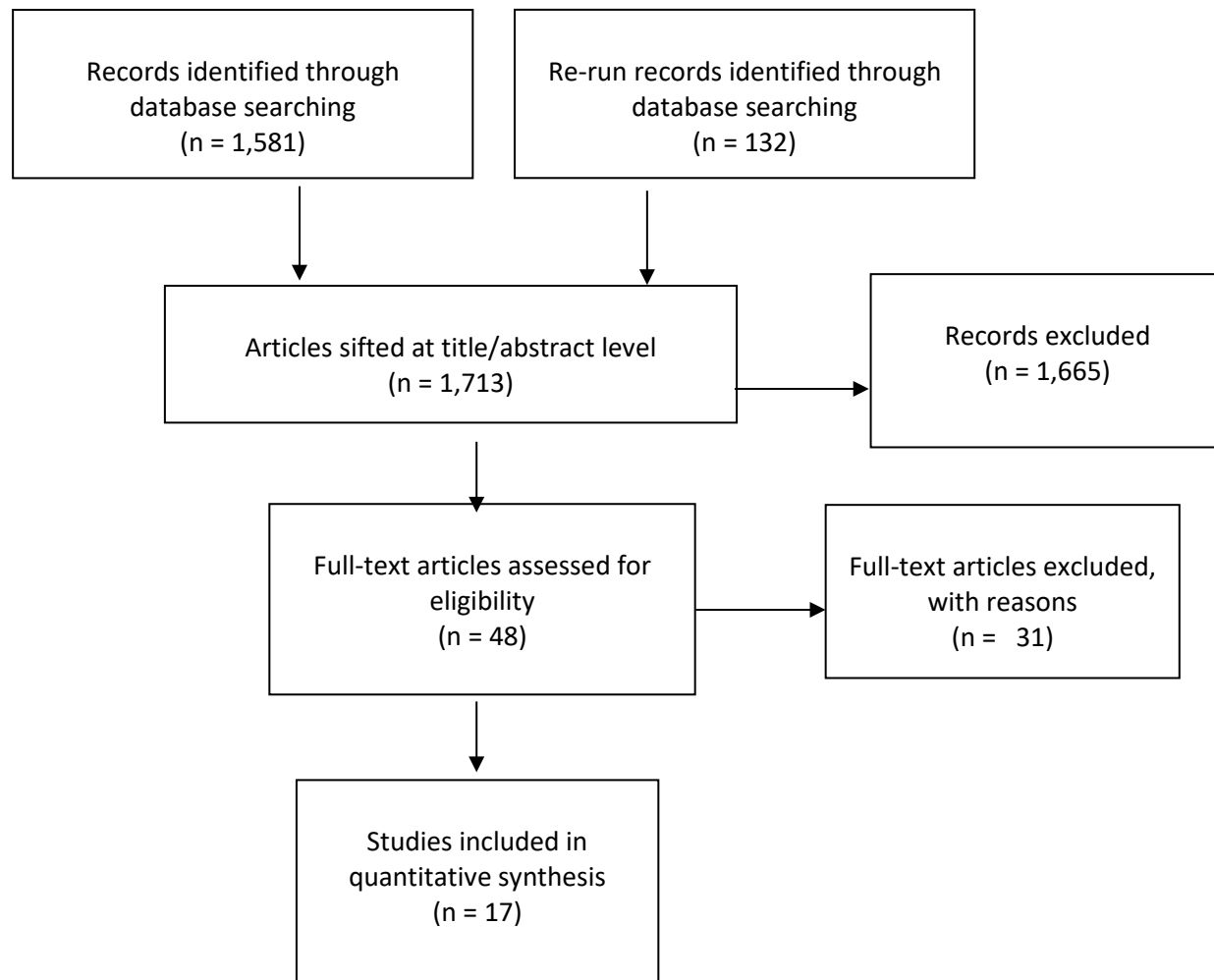
Search strategy (Medline only)

<p>Database:</p> <p>Ovid MEDLINE(R) <1946 to April 06, 2021></p>
<p>Search Strategy:</p>

-
- 1 exp Melanoma/ (97661)
 - 2 Skin Neoplasms/ (123732)
 - 3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (106805)
 - 4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (63123)
 - 5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (25578)
 - 6 (hutchinson* adj2 (freckle* or melano*)).tw. (69)
 - 7 dubreuilh*.tw. (74)
 - 8 (maligna* adj2 lentigo*).tw. (1088)
 - 9 LMM.tw. (932)
 - 10 or/1-9 (257387)
 - 11 "Margins of Excision"/ (2849)
 - 12 (excis* or margin* or surg* or remov* or resect*).tw. (2487124)
 - 13 or/11-12 (2487248)
 - 14 10 and 13 (43300)

- 15 animals/ not humans/ (4776418)
- 16 14 not 15 (41454)
- 17 limit 16 to "english language" (35325)
- 18 limit 17 to ed=20150101-20210407 (9408)
- 19 randomized controlled trial.pt. (526157)
- 20 randomi?ed.mp. (832300)
- 21 placebo.mp. (201160)
- 22 or/19-21 (885067)
- 23 18 and 22 (385)

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence

1 cm vs 2 cm

MelMarT

MelMarT

Bibliographic Reference

Moncrieff, Marc D; Gyorki, David; Saw, Robyn; Spillane, Andrew J; Thompson, John F; Peach, Howard; Oudit, Deemesh; Geh, Jenny; Dziejulski, Peter; Wilson, Ewan; Matteucci, Paolo; Pritchard-Jones, Rowan; Olofsson Bagge, Roger; Wright, Frances C; Crampton, Nic; Cassell, Oliver; Jallali, Navid; Berger, Adam; Kelly, John; Hamilton, Stephen; Durrani, Amer; Lo, Serigne; Paton, Elizabeth; Henderson, Michael A; 1 Versus 2-cm Excision Margins for pT2-pT4 Primary Cutaneous Melanoma (MelMarT): A Feasibility Study.; Annals of surgical oncology; 2018; vol. 25 (no. 9); 2541-2549

Study details

Trial registration number and/or trial name	MelMarT - NCT02385214
Study type	Randomised controlled trial (RCT)
Study location	UK, Australia, Sweden, Canada, USA
Study setting	17 centres in 5 countries.
Study dates	Recruitment between January 2015 and June 2016

Sources of funding	funded by a Grant from the Cancer Council NSW
Inclusion criteria	Melanoma characteristics Diagnosis (by shave or excision biopsy) of a primary cutaneous melanoma of Breslow thickness[1 mm (pT2a-pT4b/AJCC IB-IIC; AJCC 8th edition)
Outcome measures	<p>Quality of life "Patients' quality of life was measured using the validated FACT-M questionnaire version 4 at baseline then 3, 6, and 12 months post-randomisation"</p> <p>Neuropathic pain Neuropathic pain was measured at the same time points using the validated PainDetect questionnaire</p> <p>Health economics outcomes Health economics data (not reported in this paper) were collected in prespecified centres using EQ 5-D questionnaire with patient-specific financial questionnaires and health resource usage data.</p> <p>Surgical adverse outcomes Reconstruction rates by cohort and anatomical location</p> <p>Surgical adverse outcomes at wide excision site Including wound dehiscence; haematoma; haemorrhage; wound infection; wound necrosis; total</p>
Number of participants	400
Duration of follow-up	3, 6, and 12 months follow up
Loss to follow-up	23 were excluded post-randomisation (14 were ineligible and 9 withdrew consent)

Methods of analysis	This was an open label trial, unclear if intention to treat. Eligible patients were randomised electronically in a 1:1 fashion to either a 1 or a 2-cm wider excision margin. Patients were stratified according to age, sex, and AJCC stage (intermediate risk: IB-IIA and high risk: IIB-IIC). The database was locked and analysed according to the predesignated statistical plan once the last patient randomised had completed 12 months follow-up and completed their quality of life data (June 2017).
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Study arms

1 cm excision (N = 198)

eligible patients were randomised electronically in a 1:1 fashion to either a 1 or a 2-cm wider excision margin. In each arm, patients were staged at the same operation with sentinel lymph node biopsy (SLNB). Review of the primary melanoma histology slides was performed internally at participating institutions by designated dermatopathologists. At the time of definitive surgery, the designated margin was measured from the scar, marked, and photographed for quality assurance. The skin incision was continued vertically down through subcutaneous tissue to the deep fascia, which could be removed en bloc at the surgeon's discretion. Patients underwent direct primary closure or reconstructive surgery with a local flap or a skin graft according to the preference of the treating surgeon. Patients with positive SLNB were managed according to the treating unit's local protocol.

2 cm excision (N = 202)

Characteristics

Study-level characteristics

	Study (N = 377)
% Female	
Sample Size	n = 186 ; % = 45.5

	Study (N = 377)
Mean age (SD)	
Mean/SD	58.5 (13.15)
Mitotic rate	
Mean/SD	4.84 (5.16)
Breslow thickness	
Mean/SD	2.2 (1.28)
Ulceration	
Sample Size	n = 99 ; % = 26.3
Location	
head and neck	
Sample Size	n = 28 ; % = 7.4
Axial	
Sample Size	n = 214 ; % = 56.9
extremity	
Sample Size	n = 134 ; % = 35.6

	Study (N = 377)
Sentinel node positive	
Sample Size	n = 72 ; % = 19.1
ECOG score =1	
Sample Size	n = 19 ; % = 5.2
male	
Sample Size	n = 211 ; % = 54.5

Arm-level characteristics

	1 cm excision (N = 198)	2 cm excision (N = 202)
Mitotic rate		
Mean/SD	4.81 (5.26)	4.88 (5.07)
Breslow thickness		
Mean/SD	2.12 (1.17)	2.27 (1.39)
Ulceration		
Sample Size	n = 47 ; % = 25.4	n = 52 ; % = 27.1
Location		

	1 cm excision (N = 198)	2 cm excision (N = 202)
head and neck		
Sample Size	n = 12 ; % = 6.5	n = 16 ; % = 8.9
Axial		
Sample Size	n = 102 ; % = 55.4	n = 112 ; % = 58.3
extremity		
Sample Size	n = 70 ; % = 38	n = 64 ; % = 33.3
Sentinel node positive		
Sample Size	n = 28 ; % = 15.2	n = 44 ; % = 22.9
ECOG score = 1		
Sample Size	n = 8 ; % = 4.4	n = 11 ; % = 5.9
male		
Sample Size	n = 104 ; % = 56.2	n = 107 ; % = 55.7
Age (years)		
Mean/SD	58.7 (13.1)	58.19 (13.21)

Risk of Bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low <i>("Both cohorts were well-matched with no significant differences.")</i>
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable

Section	Question	Answer
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably no
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate <i>(Unclear if per-protocol or intention to treat analysis used. Post-randomisation dropout was low (approximately 5%) but this was largely due to ineligibility and withdrawing consent.)</i>
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No information
	2.4. Could failures in implementing the intervention have affected the outcome?	Yes

Section	Question	Answer
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No information
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Moderate <i>(little information provided about adjunctive treatments, unclear whether per protocol or intention to treat analysis was used.)</i>
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low <i>(missing data was approximately 5% post-</i>

Section	Question	Answer
		<i>randomisation, reasons for this are unlikely to be related to outcomes.)</i>
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Moderate <i>(outcome assessors were not blinded, however measures used were validated)</i>
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes

Section	Question	Answer
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate <i>(Outcome assessment was unblinded. Unclear how analysis was undertaken (e.g. per protocol or ITT), participants were excluded for ineligibility but details not provided.)</i>
	Overall Directness	Directly applicable

1 cm vs 3 cm

United Kingdom Melanoma Study Group

United Kingdom Melanoma Study Group

Bibliographic Reference

Hayes, Andrew J; Maynard, Lauren; Coombes, Gillian; Newton-Bishop, Julia; Timmons, Michael; Cook, Martin; Theaker, Jeffrey; Bliss, Judith M; Thomas, J Meirion; UK Melanoma Study, Group; British Association of, Plastic; Reconstructive and Aesthetic Surgeons, and the Scottish Cancer Therapy Network; Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: long-term follow-up of survival in a randomised trial.; The Lancet. Oncology; 2016; vol. 17 (no. 2); 184-192

Hayes AJ, Maynard L, A'Hern R, Coombes G, Newton-Bishop J, Timmons M, Cook M, Theaker J, Bliss J, Thomas JM. Long term follow up of survival in a randomised trial of wide or narrow excision margins in high risk primary melanoma. In Journal of Clinical Oncology 2015 May 20 (Vol. 33, No. 15). American Society of Clinical Oncology.

Thomas JM, et al (2004) (United Kingdom Melanoma Study Group, British Association of Plastic Surgeons, Scottish Cancer Therapy Network). Excision margins in high-risk malignant melanoma. The New England Journal of Medicine 350:757–66

Newton-Bishop, J. A., et al (2004) A quality-of-life study in high-risk (thickness ≥ 2 mm) cutaneous melanoma patients in a randomized trial of 1-cm versus 3-cm surgical excision margins. Journal of Investigative Dermatology Symposium Proceedings, 9: 152-159.

Study details

Trial registration number and/or trial name	United Kingdom Melanoma Study Group
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom
Study setting	United Kingdom
Study dates	Recruitment between January 1993 and July 2001
Sources of funding	Cancer Research UK (C588/A19167), North Thames National Health Service Executive, Northern and Yorkshire National Health Service Executive, British United Provident Association Foundation, British Association of Plastic Surgeons and the

	Meirion Thomas Cancer Research Fund. This work was supported by National Institute for Health and Research Biomedical Research Centre at The Royal Marsden NHS Foundation Trust.
Inclusion criteria	<p>Melanoma characteristics eligible patients had a single, primary, localized cutaneous melanoma 2 mm or greater in thickness on the trunk or limbs (excluding the palms of the hands or the soles of the feet), where a 3-cm excision margin was technically possible.</p> <p>Age at least 18 years old</p>
Exclusion criteria	<p>Adjunct therapy Elective lymph-node dissection, sentinel node biopsy, or adjuvant therapy was not allowed. Investigations other than chest radiography to determine the stage of disease were deemed unnecessary.</p> <p>Past medical history Patients who had a history of cancer (other than basal-cell carcinoma) or who were receiving immunosuppressive therapy were ineligible.</p> <p>Pregnancy</p>
Outcome measures	<p>Local recurrence Local recurrence was defined as a recurrence within 2 cm of the scar or graft.</p> <p>In-transit recurrence In-transit recurrence was defined as a recurrence from beyond the first 2 cm of the scar or graft to the regional nodes.</p> <p>Locoregional recurrences All locoregional recurrences were detected clinically and confirmed by biopsy.</p> <p>Recurrence-free survival</p>

	<p>Survival Measured as time from randomisation to death from any cause. Melanoma-specific survival, measured as time from randomisation to death reported to be from melanoma.</p> <p>Depression and Anxiety HAD Depression and HAD Anxiety</p> <p>Psychological Adjustment to Illness Scale Psychological Distress (PAIS), MCS, Vocational Role (PAIS), Domestic Role (PAIS), and Social Role (PAIS).</p> <p>Perception of scar Cassileth Scar score</p>
Number of participants	900
Duration of follow-up	median follow-up of 8·8 years
Loss to follow-up	<p>For overall survival, patients not known to have died were censored at the date of last follow-up. For melanoma-specific survival, patients who died of non-melanoma causes were censored at the time of death and patients who died from an unknown cause</p> <p>were censored on the day before their date of death. Both UK and non-UK patients who were not known to have died were censored at the date of their last visit. At 12 years follow up there were 23 non-censored participants remaining in the 1 cm group and 33 non-censored remaining in the 3 cm group.</p>
Methods of analysis	Authors constructed Kaplan-Meier curves and calculated HRs using a Cox proportional hazards model; they compared treatment groups using the log-rank test. Authors calculated absolute risk difference at 10 years with normal estimated 95% CIs and assessed the effect of individual prognostic factors in a multivariable analysis, adjusting for age.

HRs the probability of dying from a specific cause in 2-year intervals from randomisation if the patient was alive at the beginning of each 2-year interval, using cumulative incidence functions from the competing risks analysis. Authors did a sensitivity analysis including UK patients only.

A post-hoc subgroup analysis was performed to assess whether sex, tumour thickness, age group, site, ulceration, and proposed versus alternative pathway initial excision were associated with treatment effect. Stata 11.2 was used.

Study arms

1 cm excision margin (N = 453)

Participating surgeons chose one of two primary treatment approaches. The primary tumor could be excised before randomization, with either a 1-mm or a 1-cm margin to confirm the diagnosis and determine the thickness of the lesion. The patients were then randomly assigned to receive a 1-cm 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. The wound-closure techniques used were at the discretion of the surgeon.

3 cm excision margin (N = 447)

Participating surgeons chose one of two primary treatment approaches. The primary tumor could be excised before randomization, with either a 1-mm or a 1-cm margin to confirm the diagnosis and determine the thickness of the lesion. The patients were then randomly assigned to receive a 1-cm 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. The wound-closure techniques used were at the discretion of the surgeon.

Characteristics

Arm-level characteristics

	1 cm excision margin (N = 453)	3 cm excision margin (N = 447)
median age		
MedianIQR	58.7 (47.1 to 68.8)	58.7 (47.3 to 70.1)
male		
Sample Size	n = 248 ; % = 55	n = 220 ; % = 49
Tumour thickness (mm)		
MedianIQR	3 (2.3 to 4.2)	3.1 (2.4 to 4.5)
Tumour site		
Distal		
Sample Size	n = 136 ; % = 30	n = 140 ; % = 31
Proximal		
Sample Size	n = 108 ; % = 24	n = 97 ; % = 22
Trunk		
Sample Size	n = 203 ; % = 45	n = 206 ; % = 46

	1 cm excision margin (N = 453)	3 cm excision margin (N = 447)
Ulceration present		
Sample Size	n = 144 ; % = 32	n = 154 ; % = 35
Initial surgery		
proposed (1 mm)		
Sample Size	n = 372 ; % = 82	n = 370 ; % = 83
alternative (1 cm)		
Sample Size	n = 81 ; % = 18	n = 77 ; % = 17

Risk of Bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Yes
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low <i>(intention to treat analysis used, while 14% had protocol</i>

Section	Question	Answer
		<i>deviations, these were on the large part minor and well balanced between groups.)</i>
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low <i>("An independent data-monitoring committee regularly reviewed the trial results and reported its conclusions in a blinded fashion to the trial management group.")</i>
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Moderate <i>("There were protocol deviations in 14.0 percent of the patients; the majority were minor." "[Authors] anticipated that the three-year rate of local or in-transit recurrence in the groups as a whole would be 15 percent, but it was found to be approximately half this figure. The data-monitoring committee and the trial management group agreed that the sample size</i>

Section	Question	Answer
		<i>should be increased to 900 patients and the end points altered by combining the rates of local or in-transit recurrence with the rate of nodal recurrence into the single primary end point of locoregional recurrence."</i>)
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

Arm-level characteristics

	Nivolumab plus ipilimumab (N = 95)	Ipilimumab (N = 47)
% Female		
Sample Size	n = 32 ; % = 33.7	n = 15 ; % = 31.9
Mean age (SD)		
Custom value	Median 64 years (range 27 to 87)	Median 67 years (range 31 to 80)
AJCC stage at study entry		
Stage III		
Sample Size	n = 10 ; % = 10.5	n = 9 ; % = 19.1
Stage IV		

	Nivolumab plus ipilimumab (N = 95)	Ipilimumab (N = 47)
Sample Size	n = 85 ; % = 89.5	n = 38 ; % = 80.9
Metastasis stage at study entry		
M0		
Sample Size	n = 8 ; % = 8.4	n = 5 ; % = 10.6
M1a		
Sample Size	n = 15 ; % = 15.8	n = 8 ; % = 17
M1b		
Sample Size	n = 27 ; % = 28.4	n = 12 ; % = 25.5
M1c		
Sample Size	n = 44 ; % = 46.3	n = 21 ; % = 44.7
Not reported		
Sample Size	n = 1 ; % = 1.1	n = 1 ; % = 2.1
History of brain metastases		
Yes		
Sample Size	n = 4 ; % = 4.2	n = 0

	Nivolumab plus ipilimumab (N = 95)	Ipilimumab (N = 47)
No		
Sample Size	n = 90 ; % = 94.7	n = 47 ; % = 100
BRAF V600 Mutation		
Sample Size	n = 23 ; % = 24.2	n = 10 ; % = 21.3

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5. If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7. If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No

Section	Question	Answer
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable

Section	Question	Answer
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no

Section	Question	Answer
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1 cm vs \geq 3 cm

World Health Organization (WHO) Melanoma Group

World Health Organization (WHO) Melanoma Group

Bibliographic Reference

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Veronesi U, Cascinelli N. (1991) Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. Archives of surgery;26:438–41.

Veronesi U, et al. (1988) Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. [Erratum in: N Engl J Med 1991; 325: 292]. The New England Journal of Medicine;318(18):1159–62.

Study details

Trial registration number and/or trial name	World Health Organization (WHO) Melanoma Group
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Study type	Randomised controlled trial (RCT)
Study location	National Cancer Institute, Milan, Italy
Study setting	Multicentre, multinational trial
Study dates	Recruitment from 1980 to 1985.
Sources of funding	Fondazione Italiana per la Ricerca sul Cancro (FIRC).
Inclusion criteria	Melanoma characteristics All patients had cutaneous melanoma with ≤ 2 mm thickness on trunk or limbs (not fingers, toes, face); Age aged ≤ 65 years.
Exclusion criteria	Skin lesion characteristics Melanoma satellites, multiple primaries, Past medical history previous cancer Follow up impossible regular follow-up, Documentation inadequate histological documentation, Biopsy biopsy > 6 weeks before definite treatment

Intervention(s)	<p><u>Additional treatments</u></p> <p>Concomitant treatment was permitted with guidelines given for treatment in the first 5 years of follow-up:</p> <p>Local recurrence to be removed by wide local excision within 4 weeks of diagnosis;</p> <ol style="list-style-type: none"> 1. If nodal metastases, standard axillary/inguino-iliac node dissection within 4 weeks; 2. Adjuvant treatment could be given for after surgery for nodal metastases (defined pretrial); and 3. Distant metastases to be treated with chemotherapy, in the first instance, dacarbazine".
Outcome measures	<p>Local recurrence 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 1 cm of scar".</p> <p>Metastases 1988 paper states that 'in-transit and nodal metastases were defined as in the TNM staging system (IUAC, 1978)' The original paper recorded in-transit metastases, regional nodal metastases, and distant metastases</p> <p>Recurrence-free survival</p> <p>Survival Overall survival in the first five years of follow up, and 12 year follow up</p>
Number of participants	612
Duration of follow-up	5 years (mean duration of follow up was 55 months in both arms) and 12 year follow up in a later study

Loss to follow-up	1 person was lost to follow up, however 75 were excluded post randomisation (in total), either for not meeting eligibility criteria; or due to a mistake in treatment protocol
Methods of analysis	Rates of disease-free and overall survival were analysed by kaplan meier technique

Study arms

1 cm margin (N = 305)

Narrow excisions were performed according to the same technique; the only difference was that the cutaneous incisions were made 1 cm from the visible 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.

≥3 cm margin (N = 307)

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. 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.

Characteristics

Arm-level characteristics

	1 cm margin (N = 305)	≥3 cm margin (N = 307)
male		
Sample Size	n = 93 ; % = 30.5	n = 96 ; % = 31.3

	1 cm margin (N = 305)	≥3 cm margin (N = 307)
Site of tumour		
Trunk		
Sample Size	n = 121 ; % = 39.7	n = 119 ; % = 38.8
Upper limbs		
Sample Size	n = 60 ; % = 19.7	n = 61 ; % = 19.9
Lower limbs		
Sample Size	n = 124 ; % = 40.7	n = 127 ; % = 41.4
Age (years)		
0 - 20 years		
Sample Size	n = 6 ; % = 2	n = 0 ; % = 0
21 - 40 years		
Sample Size	n = 101 ; % = 33.1	n = 116 ; % = 37.8
41 - 50 years		
Sample Size	n = 84 ; % = 27.5	n = 75 ; % = 24.4
51 to 65 years		

	1 cm margin (N = 305)	≥3 cm margin (N = 307)
Sample Size	n = 114 ; % = 37.4	n = 116 ; % = 37.8
Thickness (mm)		
Mean/SD	0.99 (0.53)	1.02 (0.49)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Yes/Probably yes
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Yes
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Probably no
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Probably no
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High <i>(A significant number of participants were excluded following randomisation (75/612 = 12%). While the majority of these were due to non-eligibility discovered following randomisation, 15 were due to a "mistake in treatment" and 1 due to "loss to follow up". This suggests a per protocol approach to analysis. In addition, neither participants nor assessors were blinded.)</i>
Domain 2b: Risk of bias due to deviations from the intended	2.1. Were participants aware of their assigned intervention during the trial?	Yes

Section	Question	Answer
interventions (effect of adhering to intervention)		
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Moderate <i>(a significant number were excluded, but these were due to not adhering to study protocol. Participants were unblinded.)</i>
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No

Section	Question	Answer
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Probably no
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Probably no
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Probably no
	Risk-of-bias judgement for missing outcome data	Low <i>(While 12% were excluded post randomisation, the reasons for this are well explained, are unlikely to be related to study outcomes, and appear to be balanced between groups.)</i>
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Moderate <i>(outcome assessors do not appear to have been blinded to study arms)</i>
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High <i>(based on intention to treat analysis)</i>
	Overall Directness	Directly applicable

2 cm vs 4 cm

Intergroup Melanoma Surgical Trial

Intergroup Melanoma Surgical Trial

Bibliographic Reference

Balch; Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial.; Annals of surgery; 1993

Balch 2001; Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1 - 4 mm melanomas; Annals of surgical oncology

Karakousis CP, et al (1996) Local recurrence in malignant melanoma: long-term results of the multiinstitutional randomized surgical trial. Annals of surgical oncology;3:446–52.

Study details

Trial registration number and/or trial name	The Intergroup Melanoma Surgical Trial
Study type	Randomised controlled trial (RCT)
Study location	US, Canada, Denmark, South Africa
Study setting	Multicentre, trial conducted in US, Canada, Denmark, South Africa involving 93 surgeons practising in 77 centres. The Intergroup Melanoma Surgical Trial considered surgical margins of excision for primary melanomas of intermediate thickness (i.e., 1–4 mm). There were two cohorts entered into a prospective multi-institutional trial: (1) 468 patients with

	melanomas on the trunk or proximal extremity who randomly received a 2 cm or 4 cm radial excision margin and (2) 272 patients with melanomas on the head, neck, or distal extremities who received a 2 cm radial excision margin.
Study dates	Began in 1983
Sources of funding	Not reported
Inclusion criteria	Melanoma characteristics All patients had cutaneous melanoma of 1-4 mm thickness on trunk or limbs, with no evidence of metastatic melanoma in lymph nodes or distant sites Age aged 18-81 years
Exclusion criteria	Skin lesion characteristics lentigo maligna Adjunct therapy chemotherapy, radiotherapy and any other adjunct to surgery Past medical history Previous cancer
Intervention(s)	2 cm margin
Comparator	4 cm margin
Outcome measures	Local recurrence

	<p>"A local recurrence was defined as a pathologically documented melanoma that recurred within 2 cm of the surgical scar after a definitive excision of the primary melanoma. All local recurrences were treated with complete excision of the lesion. If a patient with multiple in-transit (intralymphatic) metastases had a lesion within 2 cm of the scar, it was not counted as a local recurrence. Once the patient had distant metastases, synchronous tumor recurrences in and around the surgical scar were not counted as a local recurrence because they were more likely a manifestation of distant metastasis.</p> <p>Metastases "All patients were examined for the presence of recurrent or metastatic melanoma at 3-month intervals during the first 2 postoperative years, at 6-month intervals in years 3 to 5, and annually thereafter. These surveillance examinations included a history and physical examination, chest x-rays, and measurement of serum liver enzymes; computed tomograms or nuclear scans were obtained to confirm signs or symptoms of metastatic melanoma."</p> <p>In-transit recurrence</p> <p>Recurrence-free survival Disease-free survival was calculated to the date of first recurrence</p> <p>Surgical adverse outcomes A Surgical Toxicity Form was submitted within 3 months of surgery that described the presence and severity of wound infection, wound separations, seroma or hematoma, skin graft failure, limb edema, or prolonged pain. Other surgical complications such as thrombophlebitis and pneumonia were also reported. The study also reported the skin grafting rate and the duration of hospital stay.</p> <p>Survival Survival was calculated as the months from the first surgical treatment on protocol to the last follow-up or death. Overall 5-year survival rate was reported</p>
Number of participants	470

Duration of follow-up	median 10 year follow up
Loss to follow-up	There is a 92% long-term follow-up of at least 5 years or until death
Methods of analysis	"Disease-specific survival from melanoma and disease recurrence curves were constructed by using the Kaplan-Meier product limit method. These curves were analyzed for comparisons by the log-rank procedure. Multivariate analysis based on Cox's regression model was used to associate covariates to time-dependent endpoints such as survival. Results are reported based on "randomized intent" which included those patients who refused the randomized treatment assigned."
Additional comments	Other interventions: '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'

Study arms

2 cm margin (N = 238)

"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."

4 cm margin (N = 232)

"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."

Characteristics

Arm-level characteristics

	2 cm margin (N = 238)	4 cm margin (N = 232)
male		
Sample Size	n = 57 ; % = 23.6	n = 57 ; % = 23.3
Site of primary		
Trunk		
Sample Size	n = 61 ; % = 25.2	n = 63 ; % = 25.8
Proximal extremity		
Sample Size	n = 39 ; % = 0.16	n = 37 ; % = 15.2
Thickness (mm)		
MedianIQR	1.8 (<i>empty data to empty data</i>)	1.8 (<i>empty data to empty data</i>)
Ulceration (present)		
Sample Size	n = 23 ; % = 9.5	n = 23 ; % = 9.4
Age, median (range)		
Custom value	47.6 (18 - 81)	45.3 (19 - 79.0)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes <i>("Patients are allocated into two groups by a random or chance mechanism. Patients in the first group receive standard treatment; those in the second group are asked if they will accept the experimental therapy; if they decline, they receive the best standard treatment. In the analyses of results, all those in the second group, regardless of treatment, are compared with those in the first group. Any loss of statistical efficiency can be overcome by increased numbers.")</i>
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Yes
	Risk of bias judgement for the randomisation process	Moderate <i>(Unclear if allocation concealment. A description of the randomisation process - "Patients are allocated into two groups by a random or chance mechanism. Patients in the first group receive standard treatment; those in the second group are asked if they will accept the experimental therapy; if they decline, they receive the best standard treatment. In the analyses of results, all those in the second group, regardless of treatment, are compared with those in</i>

Section	Question	Answer
		<i>the first group. Any loss of statistical efficiency can be overcome by increased numbers.")</i>
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No information
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No information
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable

Section	Question	Answer
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate <i>(Unclear if any protocol deviations or information about adherence to treatment. Intention to treat analysis was used.)</i>
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably yes
	2.5. Did study participants adhere to the assigned intervention regimen?	No information
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Moderate <i>(Per protocol analysis was not reported, unclear the extent of deviations from randomised treatment. All patients were also</i>

Section	Question	Answer
		<i>randomly selected to receive an elective lymph node dissection (ELND) or observation of their clinically uninvolved nodes as their initial management)</i>
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low <i>("Of the 486 patients entered in the study, 95.1% could be evaluated for response." "There is a 92% long-term follow-up of at least 5 years or until death.")</i>
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes

Section	Question	Answer
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low <i>("The principal investigator reviewed the circumstances and medical documentation of all deaths and was blinded as to the surgical treatment received.")</i>
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no

Section	Question	Answer
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Moderate <i>(The studies lacked detail about any protocol deviations or missing data. In addition, some outcomes were altered in one paper, but with justification "according to the protocol, local recurrence was considered as one occurring within 2 cm from the surgical scar of the first definitive operation for the primary lesion (a patient with multiple in-transit metastases and a lesion within 2-cm of the scar was not counted as a local recurrence). This is a well accepted, clinically useful, albeit biologically arbitrary definition. However, it is obvious that a recurrent lesion near the primary site may be variously classified as local recurrence or in-transit metastasis according to the definition of local recurrence. To avoid any effect the arbitrariness of the definition may have had in estimating the rates of local recurrence, in the following analysis, in addition to the local recurrence rates, the rates of in-transit metastases, combined rates of local and in-transit recurrences, and rates of distant metastases were compared between the two surgical margin groups.")</i>
Overall bias and Directness	Risk of bias judgement	Moderate
	Overall Directness	Directly applicable

Swedish Melanoma Study Group with the Danish Melanoma Group

Swedish Melanoma Study Group with the Danish Melanoma Group

Bibliographic Reference Utjes, Deborah; Malmstedt, Jonas; Teras, Juri; Drzewiecki, Krzysztof; Gullestad, Hans Petter; Ingvar, Christian; Eriksson, Hanna; Gillgren, Peter; 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: long-term follow-up of a multicentre, randomised trial.; Lancet (London, England); 2019; vol. 394 (no. 10197); 471-477

Gillgren P, Drzewiecki KT, Niin M, Gullestad HP, Hellborg H, Månsson-Brahme E, Ingvar C, Ringborg U. 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial. The Lancet. 2011 Nov 5;378(9803):1635-42.

Study details

Trial registration number and/or trial name	Swedish Melanoma Study Group in cooperation with the Danish Melanoma Group - NCT03638492.
Study type	Randomised controlled trial (RCT)
Study location	Sweden, Denmark, Estonia, and Norway.
Study setting	International trial across 53 hospitals
Study dates	recruitment between Jan 22, 1992, and May 19, 2004
Sources of funding	The Swedish Cancer Society, Stockholm Cancer Society, the Swedish Society for Medical Research, Radiumhemmet Research funds, Stockholm County Council, Wallström funds.
Inclusion criteria	Melanoma characteristics

	<p>diagnosed with localised cutaneous melanoma thicker than 2 mm, and with primary site on the trunk or upper or lower extremities</p> <p>Age aged 75 years or younger</p>
Exclusion criteria	<p>Skin lesion characteristics melanoma of the hands, feet, head and neck, and anogenital region</p> <p>Past medical history those with a history of melanoma, squamous cell carcinoma, or other known malignant disease (other than basal cell carcinoma and in-situ cancer of the cervix uteri).</p>
Outcome measures	<p>Local recurrence In the original study, recurrence-free survival and number of local recurrences were secondary endpoints, but these endpoints were not assessed in the long-term follow-up.</p> <p>Recurrence-free survival In the original study, recurrence-free survival and number of local recurrences were secondary endpoints, but these endpoints were not assessed in the long-term follow-up (Utjes 2019).</p> <p>Survival The primary outcome in this extended follow-up study was overall survival and the co-primary outcome was melanoma-specific survival. Melanoma-specific survival was measured from randomisation until death due to disease, and patients were censored at time of death if they died of non-melanoma causes or at the date of last follow-up if still alive. For calculation of overall survival, the time from randomisation until death from any cause was used.</p>

Number of participants	936
Duration of follow-up	a median follow-up of 6.7 years
Loss to follow-up	2 lost to follow up
Methods of analysis	Intention to treat

Study arms

2 cm excision margin (N = 465)

The primary excision of the tumour was done either by an excisional biopsy (margin of 1–3 mm) or with an immediate 2-cm excision margin if melanoma was strongly suspected. Patients could then be allocated to receive further surgery with a margin of up to either 2 cm or 4 cm. Patients with an initial 2-cm excision margin based on melanoma suspicion (as was done in some instances) received either no further surgery (those randomised to the 2-cm group) or an additional wide local excision with a margin up to 4 cm. Definitive surgery, if not achieved initially, was done less than 8 weeks after the date of diagnosis. Surgery extended to, or included, the deep muscle fascia, although removal of the fascia is generally no longer recommended. The pathological excision margin was not recorded.

4 cm excision margin (N = 471)

Characteristics

Arm-level characteristics

	2 cm excision margin (N = 465)	4 cm excision margin (N = 471)
male		
Sample Size	n = 289 ; % = 62	n = 311 ; % = 66
Age		
MedianIQR	59 (49 to 68)	60 (50 to 68)
Location		
neck		
Sample Size	n = 2 ; % = 1	n = 0 ; % = 0
Trunk		
Sample Size	n = 273 ; % = 59	n = 292 ; % = 62
Upper extremity		
Sample Size	n = 69 ; % = 15	n = 74 ; % = 16
Lower extremity		
Sample Size	n = 119 ; % = 26	n = 104 ; % = 22
sole of foot		
Sample Size	n = 2 ; % = 1	n = 1 ; % = 1

	2 cm excision margin (N = 465)	4 cm excision margin (N = 471)
tumour thickness		
MedianIQR	3.1 (2.5 to 4.4)	3.1 (2.5 to 4.4)
Histologenetec type		
superficial spreading melanoma		
Sample Size	n = 176 ; % = 38	n = 169 ; % = 36
lentigo maligna melanoma		
Sample Size	n = 5 ; % = 1	n = 4 ; % = 1
nodular melanoma		
Sample Size	n = 247 ; % = 53	n = 251 ; % = 53
acral lentiginous melanoma		
Sample Size	n = 1 ; % = 1	n = 1 ; % = 1
Unclassifiable		
Sample Size	n = 29 ; % = 6	n = 37 ; % = 8
data unavailable		
Sample Size	n = 7 ; % = 2	n = 9 ; % = 2

	2 cm excision margin (N = 465)	4 cm excision margin (N = 471)
Clark level of invasion		
II		
Sample Size	n = 6 ; % = 1	n = 9 ; % = 2
III		
Sample Size	n = 107 ; % = 23	n = 121 ; % = 26
IV		
Sample Size	n = 294 ; % = 63	n = 282 ; % = 60
V-		
Sample Size	n = 34 ; % = 7	n = 37 ; % = 8
data unavailable		
Sample Size	n = 24 ; % = 5	n = 22 ; % = 5
Ulceration present		
Sample Size	n = 210 ; % = 45	n = 224 ; % = 48

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable

Section	Question	Answer
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low <i>(More patients in the 2-cm group than in the 4-cm group underwent sentinel node biopsy at the time of wide local excision. The reason for this imbalance is unclear. However, a sensitivity test did not show any difference in outcome when this patient group was excluded from the analyses.)</i>
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
	2.4. Could failures in implementing the intervention have affected the outcome?	No
	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low <i>(Near the end of the enrolment period the sentinel node biopsy technique was introduced. The steering committee decided that patients who had a sentinel node biopsy should have the same follow-up as the other patients. 81 patients (9%) underwent sentinel node biopsy, 51 (23 positive nodes) in the 2-cm group and 31 (13 positive nodes) in the 4-cm group. The 36 patients with positive sentinel node biopsy were all in clinical stage IIA–C (no palpable or suspicious nodes) preoperatively and the protocol was therefore not violated.)</i>
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes

Section	Question	Answer
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Moderate
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Moderate <i>("Protocol deviations occurred in 145 (15%) of included patients (table 2). Patients who did not meet inclusion criteria after randomisation were not excluded from the study. The most common deviation was definitive surgery occurring later than 8 weeks after primary surgery. A sensitivity test detected no difference in any of the results when this patient group (74 in the 2-cm group and 71 in the 4-</i>

Section	Question	Answer
		<i>cm group) was included and excluded. One patient was randomly assigned because of high clinical suspicion of a cutaneous melanoma—ie, before a histological report was completed. Cutaneous melanoma was then ruled out but the patient was included in the analysis. 82 patients underwent sentinel node biopsy. The sensitivity analysis including and excluding these patients showed no difference in any outcome."</i>)
Overall bias and Directness	Risk of bias judgement	Moderate <i>(Lack of blinding at any point and some minor protocol deviations, as well as a greater proportion of patients in the 2cm group undergoing sentinel node biopsy, however these were unlikely to impact the results of the trial.)</i>
	Overall Directness	Directly applicable

Bergenmar 2010

Swedish Melanoma Study Group with the Danish Melanoma Group

Bibliographic Reference

Bergenmar, M., et al (2010) Surgical resection margins do not influence health related quality of life or emotional distress in patients with cutaneous melanoma: results of a prospective randomised trial. *Scandinavian Journal of Plastic & Reconstructive Surgery & Hand Surgery*, 44: 146-155.

Study details

Secondary publication of another included study- see primary study for details	Seems to be related to the study by Utjes 2019, but unclear
Other publications associated with this study included in review	<p>Utjes, Deborah; Malmstedt, Jonas; Teras, Juri; Drzewiecki, Krzysztof; Gullestad, Hans Petter; Ingvar, Christian; Eriksson, Hanna; Gillgren, Peter; 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: long-term follow-up of a multicentre, randomised trial.; Lancet (London, England); 2019; vol. 394 (no. 10197); 471-477</p> <p>Gillgren P, Drzewiecki KT, Niin M, Gullestad HP, Hellborg H, Månsson-Brahme E, Ingvar C, Ringborg U. 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial. The Lancet. 2011 Nov 5;378(9803):1635-42.</p>
Trial registration number and/or trial name	Unclear "prospective randomised Scandinavian trial"
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Stockholm County
Study dates	March 1994 to November 2005
Sources of funding	This study was supported by a grant from the Cancer Society in Stockholm.
Inclusion criteria	<p>Melanoma characteristics</p> <p>A histologically-confirmed diagnosis of cutaneous malignant melanoma more than 2.00 mm thick (T3–T4), situated on the trunk or extremities (except hands and feet).</p> <p>Age</p> <p>up to 75 years of age</p>
Exclusion criteria	Past medical history

	<p>previous malignant disease except basal cell carcinoma</p> <p>Metastases</p> <p>melanoma satellites or metastatic disease</p>
Intervention(s)	
Comparator	
Outcome measures	<p>Quality of life</p> <p>The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) is a tool for measurement of health-related QoL in patients with cancer in clinical trials, which was developed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group. Both versions consist of 30 items constituting nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea/vomiting); and three global health and QoL items. A number of single item scales are also included. The respondents are asked to indicate for each item the extent to which he or she has experienced the problem during the past week on a four-point scale from 1 ("Not at all") to 4 ("Very much"). Two items that constitute the global quality of life scale have seven response categories. Variables not considered to be affected by resection margins were excluded (nausea/vomiting, dyspnoea, constipation, and diarrhoea).</p> <p>Depression and Anxiety</p> <p>The Hospital Anxiety and Depression Scale (HAD) is a self-administered questionnaire used extensively in patients with cancer. It consists of 14 items, 7 that assess anxiety (HAD-A) and 7 that assess depression (HAD-D). Cut-off points that identify clinical cases of anxiety disorders or depression, or both, among somatically ill, non-psychiatric patients have been established.</p> <p>Impact of event</p> <p>The Impact of Event Scale (IES) is a 15-item scale for the assessment of post-traumatic stress responses including two subscales: intrusive thoughts and images (intrusion), and avoidance or denial behaviour (avoidance). The patients indicate on a four graded scale to what extent their experiences during the last week have corresponded to experiences described in each statement. Responses are weighted (the lowest score is given the value of 0, the next 1, the third 3, and the fourth 5) and coded into two sets of sums, which give a maximum of 40 for avoidance and of 35 for intrusion.</p>
Number of participants	165
Duration of follow-up	3, 9, and 15 months after inclusion

Loss to follow-up	Four patients were excluded from the health related QoL study (two declined to participate, one had a psychiatric diagnosis, and one was included in another clinical trial). As a result of administrative failure, a total of 17 patients were not informed about the health-related QoL study and hence not included. By 15 months follow up only 102 (88%) were left in the trial. Unclear how loss to follow up differed between experimental arms . Of the 144 patients included, 28 were excluded during the study period, because of: recurrence of melanoma (n = 20) "as one would expect a recurrence to adversely affect both quality of life and to increase emotional distress"; a new diagnosis of cancer (n = 3); inclusion in another clinical trial (n = 2); death (n = 2); and one patient who had moved outside the catchment area.
Methods of analysis	modified intention to treat

Study arms

2-cm excision (N = 70)

Loss to follow-up	Four patients were excluded from the health related QoL study (two declined to participate, one had a psychiatric diagnosis, and one was included in another clinical trial). As a result of administrative failure, a total of 17 patients were not informed about the health-related QoL study and hence not included.
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4-cm excision (N = 74)

Loss to follow-up	Four patients were excluded from the health related QoL study (two declined to participate, one had a psychiatric diagnosis, and one was included in another clinical trial). As a result of administrative failure, a total of 17 patients were not informed about the health-related QoL study and hence not included.
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Characteristics

Arm-level characteristics

	2-cm excision (N = 70)	4-cm excision (N = 74)
Male		
Sample Size	n = 53 ; % = 76	n = 56 ; % = 76
Age at diagnosis		
MedianIQR	61.5 (23 to 75)	59.5 (21 to 75)
Type of closure		

	2-cm excision (N = 70)	4-cm excision (N = 74)
Primary closure		
Sample Size	n = 57 ; % = 81	n = 26 ; % = 35
Skin graft		
Sample Size	n = 11 ; % = 16	n = 40 ; % = 54
Skin flap		
Sample Size	n = 2 ; % = 3	n = 8 ; % = 11

Risk of Bias

ction	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	No information
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No information
	Risk of bias judgement for the randomisation process	High <i>(The first assessment was done before randomisation. Unclear how randomisation was performed. Unclear if allocation concealment. Very few baseline characteristics were reported with which to assess the success of randomisation.)</i>
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes

Question	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No information
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No information
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Probably yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate <i>(Unclear if any deviations from intended intervention)</i>
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No information
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No information

Question	Question	Answer
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No information
	Risk-of-bias judgement for missing outcome data	High <i>(By the end of follow up the amount of missing data was significant (88%). It is unclear how the extent of missing data varied between arms. Following randomisation, 17 patients were not informed about the health-related QoL study and hence not included. Following intervention, 28 were excluded during the study period, because of: recurrence of melanoma (n = 20) as one would expect a recurrence to adversely affect both quality of life and to increase emotional distress; a new diagnosis of cancer (n = 3); inclusion in another clinical trial (n = 2); death (n = 2); and one patient who had moved outside the catchment area.)</i>
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low

Question	Question	Answer
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Moderate <i>(Insufficient justification or detail for methods provided and protocol is not cited.)</i>
Overall bias and Directness	Risk of bias judgement	High
	Overall Directness	Directly applicable

2 cm vs ≥ 5 cm

Swedish Melanoma Study Group

Swedish Melanoma Study Group

Bibliographic Reference

Cohn-Cedermark G EA; Long term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0.8-2.0 mm.; Cancer; 2000

Ringborg U, et al. (1996) Resection margins of 2 versus 5 cm for cutaneous malignant melanoma with a tumor thickness of 0.8 to 2.0 mm: randomized study by the Swedish Melanoma Study Group. *Cancer* 77:1809–14.

Bergenmar, M., et al (2008) Health related quality of life in patients with malignant melanoma included in a randomized study of resection margins. *Pigment Cell & Melanoma Research*, 21: 333.

Study details

Trial registration number and/or trial name	Swedish Melanoma Study Group
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Multicentre trial conducted in Sweden in 5 regional oncologic centres/ 39 clinics (38 hospitals)
Study dates	recruitment from 1982 to 1991
Sources of funding	Supported by grants from the Cancer Society in Stockholm and the King Gustaf V Jubilee Fund.
Inclusion criteria	Melanoma characteristics All patients had cutaneous melanoma with $> 0.8 \text{ mm} \leq 2 \text{ mm}$ thickness on trunk or extremity (not fingers, feet, face); Age any age
Exclusion criteria	Past medical history

	<p>previous cancer</p> <p>Metastases Melanoma satellites, metastatic disease</p>
Intervention(s)	<p><u>Additional treatment</u></p> <p>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.</p>
Comparator	
Outcome measures	<p>Local recurrence Local recurrence was defined as a recurrence in the 'scar or transplant'. Other forms of recurrence are not defined. Clinical follow-up information was obtained through the clinical records. The identification of previous and secondary tumors was done by a search of the files of the Swedish National Cancer Registry.</p> <p>Metastases Regional skin metastasis; Regional lymph node recurrence; Distant metastasis</p> <p>Recurrence-free survival Clinical follow-up information was obtained through the clinical records. The identification of previous and secondary tumors was done by a search of the files of the Swedish National Cancer Registry.</p> <p>Survival Information on vital status was checked against the Swedish Cause-of-Death Registry. Includes overall survival and melanoma-specific survival.</p> <p>Any recurrence</p>

Number of participants	989
Duration of follow-up	Duration of follow-up: 11 years overall survival), 8 years (recurrence-free survival). Patients were scheduled for a clinical follow-up visit every 3 months for 3 years and thereafter every 6 months for 2 years. After 5 years, patients were followed according to local tradition.
Loss to follow-up	five patients were lost to follow-up prior to death due to emigration (1–4 years after primary treatment).
Methods of analysis	<p>"When analyzing the different types of first events, patients were considered to be at risk of the studied event until the first of the events defining recurrent disease occurred or, in the absence of an event, until the end of follow-up. The occurrence of any other event was treated as a censored observation at the time of its occurrence. The OS and RFS rates were estimated using the Kaplan–Meier method. Distributional comparisons were made using a two-tailed log rank test.</p> <p>Hazards rate ratios and 95% confidence intervals were estimated using the Cox proportional hazards regression model, stratified by region, with wide excision as the reference group.¹³ All analyses were based on “intention to treat” and were performed separately for all randomized patients (n = 989 patients) as well as for all eligible patients (n 5 895 patients). In the analysis of the eligible patients, potential confounding from other well-documented risk factors, such as gender, age (< 40 years, 40–59 years, and ≥ 60 years), and tumor thickness (< 1.0 mm, 1.0 –1.4 mm, and ≥ 1.5 mm) was studied by including these factors, as well as treatment, in the regression models."</p>
Additional comments	

Study arms

2 cm margin (N = 476)

Definite surgical treatment was to be performed within 6 weeks of the primary diagnostic procedure.

≥5 cm margin (N = 513)

Definite surgical treatment was to be performed within 6 weeks of the primary diagnostic procedure. All initially received 2 cm margin, then those randomised to wide excision received secondary procedure within 6 weeks.

Characteristics**Arm-level characteristics**

	2 cm margin (N = 476)	≥5 cm margin (N = 513)
Age (mean)		
Custom value	52.3	51.4
male		
Sample Size	n = 225 ; % = 47	n = 246 ; % = 48
Margin of excision (mean)		
Custom value	2	4.5
Site of tumour		
Trunk		

	2 cm margin (N = 476)	≥5 cm margin (N = 513)
Sample Size	n = 265 ; % = 56	n = 282 ; % = 55
Lower extremity		
Sample Size	n = 140 ; % = 29	n = 150 ; % = 29
Upper extremity		
Sample Size	n = 61 ; % = 13	n = 75 ; % = 15
Head/neck		
Sample Size	n = 6 ; % = 1	n = 3 ; % = 0.4
Hand		
Sample Size	n = 2 ; % = 0.4	n = 1 ; % = 0.2
Foot		
Sample Size	n = 2 ; % = 0.4	n = 2 ; % = 0.4
Tumour thickness (mm, median (max-min))		
Custom value	1.2 (0.4 to 2.9)	1.2 (0.3 to 2.0)
Histological type of melanoma (%)		
superficial spreading melanoma		

	2 cm margin (N = 476)	≥5 cm margin (N = 513)
Sample Size	n = 371 ; % = 78	n = 404 ; % = 79
nodular melanoma		
Sample Size	n = 63 ; % = 13	n = 67 ; % = 13
lentigo maligna melanoma		
Sample Size	n = 0 ; % = 0	n = 4 ; % = 1
acral lentiginous melanoma		
Sample Size	n = 4 ; % = 1	n = 2 ; % = 0.4
unclassifiable melanoma		
Sample Size	n = 21 ; % = 4	n = 18 ; % = 4
melanoma in situ		
Sample Size	n = 0 ; % = 0	n = 1 ; % = 0.2
Clark level of invasion		
I-		
Sample Size	n = 0 ; % = 0	n = 1 ; % = 0.2
II		

	2 cm margin (N = 476)	≥5 cm margin (N = 513)
Sample Size	n = 53 ; % = 11	n = 80 ; % = 16
III		
Sample Size	n = 297 ; % = 62	n = 304 ; % = 59
IV		
Sample Size	n = 114 ; % = 24	n = 120 ; % = 23
V-		
Sample Size	n = 1 ; % = 0.2	n = 0 ; % = 0
Ulceration (present)		
Sample Size	n = 36 ; % = 18	n = 33 ; % = 17

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes

Section	Question	Answer
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Yes
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Probably no
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes

Section	Question	Answer
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate <i>("The median resection margin in the narrow excision group was 2 cm (range, 0.2–5.5 cm), and it was 5 cm (range, 0.2–10.0 cm) in the wide excision group (mean resection margin, 2.1 cm vs. 4.6 cm). Seventy-five percent of the patients in each treatment group were treated with the exact allocated excision margin." However, it is unclear whether deviations from the intended interventions was as a result of the experimental context. Intention to treat analysis was used. Deviations appeared to be balanced between groups.)</i>
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No information

Section	Question	Answer
	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
	2.5. Did study participants adhere to the assigned intervention regimen?	No
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High <i>(The median resection margin in the narrow excision group was 2 cm (range, 0.2–5.5 cm), and it was 5 cm (range, 0.2–10.0 cm) in the wide excision group (mean resection margin, 2.1 cm vs. 4.6 cm). Seventy-five percent of the patients in each treatment group were treated with the exact allocated excision margin.)</i>
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable

Section	Question	Answer
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low <i>(All analyses were on an intent-to treat basis; however, separate analyses also were done excluding the ineligible patients, leading to identical conclusions. Patients were ineligible for not meeting inclusion criteria following randomisation.)</i>
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	Risk-of-bias judgement for measurement of the outcome	Moderate <i>(outcome assessors were unblinded, and for some outcomes e.g. local recurrence, regional cutaneous metastasis, and regional lymph node metastasis, it was unclear which definitions were used.)</i>
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate <i>(high risk of bias for assessing per-protocol)</i>
	Overall Directness	Directly applicable

Large European Multicentric Phase III Study (French Study)

Large European Multicentric Phase III Study (French Study)

Bibliographic Reference

Khayat D, Rixe O, Martin G, Soubrane C, Banzet M, Bazex JA, Lauret P, Vérola O, Auclerc G, Harper P, Banzet P. Surgical margins in cutaneous melanoma (2 cm versus 5 cm for lesions measuring less than 2.1-mm thick) Long-term results of a large European multicentric phase III study. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2003 Apr 15;97(8):1941-6.

Banzet P, Thomas A, Vuillemin E. Wide versus narrow surgical excision in thin (< 2 mm) stage I primary cutaneous malignant melanoma: long term results of a French multicentric prospective randomized trial on 319 patients. *InProc Am Assoc Clin Oncol* 1993 (Vol. 12, p. 387).

Study details

Trial registration number and/or trial name	Large European Multicentric Phase III Study (French Study)
Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	Multicentre trial undertaken in Europe.
Study dates	initiated in 1981
Sources of funding	Supported by the Association Pour la Vie-Espoir Contre le Cancer (A.V.E.C.).
Inclusion criteria	Melanoma characteristics All patients had melanoma with ≤ 2 mm thickness on trunk, limbs, head and neck (not fingers, toes, nails); TNM stage 1; Age

	aged < 70 years.
Exclusion criteria	Skin lesion characteristics Melanomas arising from melanosis, lentigo, acral lesions.
Intervention(s)	<u>Adjunctive therapy</u> 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)
Outcome measures	Local recurrence Local disease recurrence defined as recurrence within 2 cm of the scar Metastases In-transit metastases was defined as disease recurrence between the primary tumour site and the regional lymph node Survival Overall survival and progression free survival. Survival times were calculated from the date of inclusion until death. Time to disease progression was calculated.

Number of participants	337
Duration of follow-up	16 years
Loss to follow-up	median follow-up of 192 months (range, 2–228 months).
Methods of analysis	The survival analysis (overall survival and progression-free survival) was performed using the actuarial Kaplan–Meier method and differences between the curves were analyzed using the log rank test. The Cox proportional hazards model was used to evaluate prognostic factors and contingency tables were analyzed by an appropriate chi-square test or exact t test.

Study arms

2 cm margin (N = 167)

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.

≥5 cm margin (N = 170)

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.

Characteristics

Study-level characteristics

	Study (N =)
male	
Sample Size	n = 122 ; % = 37.4
Location of tumour	
head and neck	
Sample Size	n = 16 ; % = 4.9
Trunk	
Sample Size	n = 93 ; % = 28.5
Upper extremity	
Sample Size	n = 68 ; % = 20.8
Lower extremity	
Sample Size	n = 138 ; % = 42.3
Other	
Sample Size	n = 5 ; % = 1.5
Clark level of invasion	
I-	

	Study (N =)
Sample Size	n = 1 ; % = 0
II	
Sample Size	n = 54 ; % = 16.6
III	
Sample Size	n = 181 ; % = 55.5
IV	
Sample Size	n = 80 ; % = 24.5
Histology	
superficial spreading	
Sample Size	n = 281 ; % = 86.2
nodular	
Sample Size	n = 41 ; % = 12.6
no class	
Sample Size	n = 3 ; % = 0
Breslow thickness (mm)	

	Study (N =)
<= 0.5	
Sample Size	n = 4 ; % = 0.1
0.51 to 1.0	
Sample Size	n = 34 ; % = 10.4
1.01 to 1.5	
Sample Size	n = 27 ; % = 8.3
>=1.51	
Sample Size	n = 20 ; % = 6.1

Arm-level characteristics

	2 cm margin (N = 167)	≥5 cm margin (N = 170)
Breslow thickness (mm)		
<= 0.5		
Sample Size	n = 8 ; % = 4.9	n = 10 ; % = 6
0.51 to 1.0		
Sample Size	n = 72 ; % = 44.7	n = 69 ; % = 41.8

	2 cm margin (N = 167)	≥5 cm margin (N = 170)
1.01 to 1.5		
Sample Size	n = 51 ; % = 31.6	n = 55 ; % = 33.3
>=1.51		
Sample Size	n = 30 ; % = 18.6	n = 31 ; % = 18.8
male		
Sample Size	n = 61 ; % = 37.9	n = 61 ; % = 37
Location of tumour		
head and neck		
Sample Size	n = 10 ; % = 6.2	n = 6 ; % = 3.6
Trunk		
Sample Size	n = 47 ; % = 57.8	n = 46 ; % = 27.9
Upper extremity		
Sample Size	n = 32 ; % = 42.2	n = 36 ; % = 21.8
Other		
Sample Size	n = 5 ; % = 3.1	n = 0 ; % = 0

	2 cm margin (N = 167)	≥5 cm margin (N = 170)
Lower extremity		
Sample Size	n = 55 ; % = 34.2	n = 73 ; % = 44.2
Clark level of invasion		
I-		
Sample Size	n = 1 ; % = 0	n = 0 ; % = 0
II		
Sample Size	n = 24 ; % = 14.9	n = 35 ; % = 21.2
III		
Sample Size	n = 93 ; % = 57.7	n = 90 ; % = 54.5
IV		
Sample Size	n = 42 ; % = 26.1	n = 39 ; % = 23.6
Histology		
superficial spreading		
Sample Size	n = 139 ; % = 86.3	n = 142 ; % = 86.1
nodular		

	2 cm margin (N = 167)	≥5 cm margin (N = 170)
Sample Size	n = 21 ; % = 13	n = 20 ; % = 12.1
no class		
Sample Size	n = 0 ; % = 0	n = 2 ; % = 0.1

Risk of Bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Probably yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Moderate <i>(unclear if allocation concealment)</i>
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes

Section	Question	Answer
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Probably yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate <i>(a likely modified intention to treat was used, however there was a lack of information about any deviations from treatment protocol or the reasons for loss to follow up)</i>

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably yes
	2.5. Did study participants adhere to the assigned intervention regimen?	No information
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High <i>(there was a lack of information about adherence to intervention)</i>
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No

Section	Question	Answer
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Probably yes
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Probably no
	Risk-of-bias judgement for missing outcome data	Low <i>("After nearly 20 years of follow-up, 40 patients (12%) were lost to follow-up. Another 36 patients had missing information regarding the date of their tumor recurrences. However, their death certificate data were evaluable for survival analysis (17 patients in the limited excision arm and 19 in the wide excision arm). Therefore, 243/326 patients were evaluable for disease-free survival and 286/326 patients were evaluable for survival (139 for the 2-cm margin and 147 for the 5-cm margin)." The reasons for loss to follow up/missing data were unclear.")</i>
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No

Section	Question	Answer
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Moderate <i>(Outcome assessors did not appear to be blinded)</i>
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no

Section	Question	Answer
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High <i>(Non-blinded assessments. Unclear approach to analysis (e.g. intention to treat). Unclear approach to randomisation or allocation concealment. Large attrition/missing data at 20 years follow up.)</i>
	Overall Directness	Directly applicable

Appendix E - Forest plots

No forest plots were generated from the evidence review as meta-analysis was not possible.

Appendix F – GRADE tables

1 cm vs 2 cm excision

Quality of life

Table 4 Quality of life

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Quality	
				Indirectness	Inconsistency	Imprecision		
Quality of life over 12 months post-randomisation measured using the FACT-M questionnaire (version 4) (HR<1 favours narrow excision margin)								
Moncrieff 2018 (MelMarT)	377	N/A	<i>“there was no difference in quality of life or neuropathic pain data in any domain between the 1 and 2-cm groups. Similarly, there were no differences between the two margins in any subgroup analyses.”</i>	Serious ¹	Not serious	N/A	NE ²	Low
<ol style="list-style-type: none"> 1. Study was at serious risk of bias and was marked down one level: Outcome assessment was unblinded. Unclear how analysis was undertaken (e.g. per protocol or participants were excluded for ineligibility but details not provided). 2. It was not possible to estimate imprecision as results were reported graphically, therefore the study was marked down one level for quality. 								

Reconstructive surgery

Table 5 Reconstruction

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Quality	
				Indirectness	Inconsistency	Imprecision		
Reconstruction surgery at 12 months post-randomisation (OR<1 favours narrow excision margin)								
Moncrieff 2018 (MelMarT)	377	N/A	OR 0.29 [0.18, 0.49]	Serious ¹	Not serious	N/A	Not Serious	Moderate
1. Study was at serious risk of bias and was marked down one level: Outcome assessment was unblinded. Unclear how analysis was undertaken (e.g. per protocol or participants were excluded for ineligibility but details not provided).								

Surgical adverse events

Table 6 Surgical adverse events

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Quality
				Indirectness	Inconsistency	Imprecision	
Total surgical adverse events including: wound dehiscence; haematoma; haemorrhage; wound infection; or wound necrosis post-intervention (OR<1 favours narrow excision margin)							

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Moncrieff 2018 (MelMarT)	377	N/A	OR 0.89 [0.46, 1.70]	Serious ¹	Not serious	N/A	Very Serious ²	Very Low
Wound dehiscence post intervention (OR<1 favours narrow excision margin)								
Moncrieff 2018 (MelMarT)	377	N/A	OR 1.04 [0.26, 4.24]	Serious ¹	Not serious	N/A	Very Serious ²	Very Low
Haematoma (Grade I or IIIa) post intervention (OR<1 favours narrow excision margin)								
Moncrieff 2018 (MelMarT)	377	N/A	OR 1.57 [0.26, 9.53]	Serious ¹	Not serious	N/A	Very Serious ²	Very Low
Haemorrhage post intervention (OR<1 favours narrow excision margin)								
Moncrieff 2018 (MelMarT)	377	N/A	No participants experienced haemorrhage (effect size not estimable)	Serious ¹	Not serious	N/A	Very Serious ²	Very Low
Wound infection (Grade I or II) post intervention (OR<1 favours narrow excision margin)								
Moncrieff 2018 (MelMarT)	377	N/A	OR 1.29 [0.52, 3.20]	Serious ¹	Not serious	N/A	Very Serious ²	Very Low
Wound necrosis (including partial/total loss of skin graft) post intervention (OR<1 favours narrow excision margin)								
Moncrieff 2018 (MelMarT)	377	N/A	OR 0.14 [0.02, 1.19]	Serious ¹	Not serious	N/A	Serious ³	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<ol style="list-style-type: none"> 1. Study was at serious risk of bias and was marked down one level: Outcome assessment was unblinded. Unclear how analysis was undertaken (e.g. per protocol or participants were excluded for ineligibility but details not provided). 2. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for odds ratios) 3. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for odds ratios) 								

1 cm vs 3 cm

Mortality rate and survival

Table 7 Deaths/survival over follow up

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Deaths due to any cause (follow up was 68 months [IQR 35–103]) (HR<1 favours narrow excision margin)								
Hayes 2016 (UK-MSG)	900	N/A	HR 1.14 [95% CI 0.96–1.36] ¹	Not Serious	Not serious	N/A	Serious ²	Moderate
Deaths due to any cause (median follow up 60 months – HR<1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Imprecision	Quality
				Indirectness	Inconsistency			
Thomas 2004 (UK-MSG)	900	N/A	HR 1.07 (0.85–1.36)	Not Serious	Not serious	N/A	Serious ²	Moderate
Melanoma-specific deaths over follow up (follow up was 68 months [IQR 35–103]) (HR<1 favours narrow excision margin)								
Hayes 2016 (UK-MSG)	900	N/A	HR 1.24 [95% CI 1.01–1.53]¹	Not Serious	Not serious	N/A	Serious ²	Moderate
Melanoma-specific deaths (median follow up 60 months – HR<1 favours narrow excision margin)								
Thomas 2004 (UK-MSG)	900	N/A	HR 1.24 (0.96–1.61)	Not Serious	Not serious	N/A	Serious ²	Moderate
Overall Survival over follow up (follow up was 68 months [IQR 35–103]) (HR<1 favours narrow excision margin)								
Hayes 2016 (UK-MSG)	773	Participants for whom all known prognostic factors were available	HR 1.19 (0.99–1.45) ³	Not Serious	Not serious	N/A	Serious ²	Moderate
Melanoma-specific survival over follow up (follow up was 68 months [IQR 35–103]) (HR<1 favours narrow excision margin)								
Hayes 2016 (UK-MSG)	773	Participants for whom all known prognostic factors	HR 1.28 (1.02–1.61)³	Not Serious	Not serious	N/A	Serious ²	Moderate

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		were available						
1. Unadjusted 2. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for hazard ratios) 3. Adjusted for sex, tumour thickness, ulceration, site, and age (greater than 60 years)								

Locoregional recurrence

Table 8 Locoregional recurrence

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Locoregional recurrence (median follow up 60 months – HR<1 favours narrow excision margin): Local recurrence was defined as a recurrence within 2 cm of the 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 clinically and confirmed by biopsy.								
Thomas 2004 (UK-MSG)	900	N/A	HR 1.26 (1.00 to 1.59)	Serious ³	Not serious	N/A	Serious ¹	Low
Recurrence or death (median follow up 60 months – HR<1 favours narrow excision margin): defined as above								
Thomas 2004 (UK-MSG)	900	N/A	HR 1.21 (0.99 to 1.46)	Not Serious	Not serious	N/A	Serious ¹	Moderate
Local or in-transit recurrence (median follow up 60 months – HR<1 favours narrow excision margin): defined as above								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Thomas 2004 (UK-MSG)	900	N/A	HR 1.51 (0.91 to 2.51)	Not Serious	Not serious	N/A	Serious ¹	Moderate
Regional -node recurrence (median follow up 60 months – HR<1 favours narrow excision margin): defined as above								
Thomas 2004 (UK-MSG)	900	N/A	HR 1.21 (0.96–1.53)	Not Serious	Not serious	N/A	Serious ¹	Moderate
<ol style="list-style-type: none"> 1. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for hazard ratios) 2. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for odds ratios) 3. Study was marked down one level for risk of bias for this outcome as it was calculated by combining the rates of local or in-transit recurrence with the rate of nodal recurrence into the single primary end point, and that this was a protocol deviation that occurred once the study was underway. 								

Quality of life scores

Table 9 quality of life scores

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Physical component summary score (maximum follow up time = 2 years; coefficient<0 favours narrow excision margin): measured using the Medical Outcomes Short Form (MOS-SF36)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Newton-Bishop 2004 (UK-MSG)	392	Subgroup study of participants who were sent a series of QoL-related questionnaires	Coefficient= – 157.0, SE= 83.5, p=0.06 ¹	Very Serious ²	Not serious	N/A	NE ³	Very Low
Mental component summary score (maximum follow up time = 2 years; coefficient<0 favours narrow excision margin): measured using the Medical Outcomes Survey–Short Form (MOS-SF36). Lower scores indicate better outcomes.								
Newton-Bishop 2004 (UK-MSG)	392	Subgroup study of participants who were sent a series of QoL-related questionnaires	Coefficient= – 133.1, SE= 91.6, p=0.15 ¹	Very Serious ²	Not serious	N/A	NE ³	Very Low
“Poor” vocational adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined.								
Newton-Bishop 2004 (UK-MSG)	426	Subgroup study of participants who were sent a series of QoL-related questionnaires	OR 1.66 (0.68 to 4.08) ¹	Very Serious ²	Not serious	N/A	Serious ⁴	Very Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
“Poor” domestic adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined.								
Newton-Bishop 2004 (UK-MSG)	426	Subgroup study of participants who were sent a series of QoL-related questionnaires	OR 3.11 (1.17–8.27) ¹	Very Serious ²	Not serious	N/A	Serious ⁵	Very Low
“Poor” sexual adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined.								
Newton-Bishop 2004 (UK-MSG)	426	Subgroup study of participants who were sent a series of QoL-related questionnaires	OR 1.92 (0.70–5.31) ¹	Very Serious ²	Not serious	N/A	Serious ⁴	Very Low
“Poor” extended family adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined.								
Newton-Bishop 2004 (UK-MSG)	426	Subgroup study of participants who were sent a series of	OR 1.09 (0.43–2.75) ¹	Very Serious ²	Not serious	N/A	Serious ⁴	Very Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		QoL-related questionnaires						
“Poor” social adjustment to illness (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the Psychological adjustment to illness scale (PAIS), unclear how poor was defined.								
Newton-Bishop 2004 (UK-MSG)	426	Subgroup study of participants who were sent a series of QoL-related questionnaires	OR 4.22 (1.54–11.55)¹	Very Serious ²	Not serious	N/A	Not Serious	Low
Perception of scar (maximum follow up time = 2 years; OR>1 favours narrow excision margin): measured using the last Cassileth Scar score on follow up								
Newton-Bishop 2004 (UK-MSG)	128	Subgroup study of participants who were sent a series of QoL-related questionnaires	OR 5.55 (2.06–14.98)	Very Serious ²	Not serious	N/A	Not Serious	Low
<ol style="list-style-type: none"> Adjusted for time of follow up, sex, age, and whether the scar was exposed. Study was marked down twice for very serious risk of bias. This study represented a significant subsample of the original randomised controlled trial including only participants from non-overseas centres, participating centres, or those centres who recruited participants after this study was finished. Of those sent questionnaires 757 responded. Non-responders were more likely to be women or enrolled prospectively. “Of the 757 questionnaires returned, there were 82 missing PCS and MCS scores, 28 missing scar scores, and between 28 and 252 missing observations over all PAIS domain scores. The missing PAIS domain scores related mainly to vocational and social function. The number responding at a particular time point of follow up varied (follow up was at <1 month, 1 month, 3 months, 6 months, 1 year, and 2 years, particip 								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
could be contacted multiple times). To determine whether the effect of time on the PCS and MCS differed between margin groups, random effects models were used incorporating time as a continuum in years and an interaction term between margin and time. No blinding.								
3. It was not possible to estimate imprecision, study was marked down one level accordingly								
4. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for odds ratios)								
5. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for odds ratios)								

Surgical adverse events

Table 10 Surgical adverse events

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Total surgical complications: not defined								
Hayes 2016 (UK-MSG)	900	N/A	OR 0.49 [0.32, 0.76]	Not Serious	Not serious	N/A	Not Serious	High
Partial or complete graft loss post intervention (OR<1 favours narrow excision margin)								
Hayes 2016 (UK-MSG)	900	N/A	OR 0.48 [0.22, 1.04]	Not Serious	Not serious	N/A	Serious ¹	Moderate

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Wound dehiscence post intervention (OR<1 favours narrow excision margin)								
Hayes 2016 (UK-MSG)	900	N/A	OR 0.76 [0.28, 2.07]	Not Serious	Not serious	N/A	Very Serious ²	Low
1. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for odds ratios) 2. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for odds ratios)								

1 cm vs ≥ 3 cm*Local, regional, and distant recurrence*

Table 11 Recurrence

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Recurrence-free survival at a median follow-up of 55 months (OR>1 favours narrow excision margin)								
Veronesi 1988 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 1.12 [0.64, 1.95]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Recurrence-free survival over 8-years follow up (OR>1 favours narrow excision margin)								
Veronesi 1991 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 0.82 [0.54, 1.26]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Local recurrence at a mean follow up of 55 months (OR<1 favours narrow excision margin)								
Veronesi 1988	612	N/A	OR 7.12 [0.37, 138.34]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
(World Health Organisation (WHO) melanoma group)								
Local recurrence (first recurrence) at 8 years (OR<1 favours narrow excision margin)								
Veronesi 1991 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 9.18 [0.49, 171.23]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
In-transit metastases at a mean follow up of 55 months (OR<1 favours narrow excision margin)								
Veronesi 1988 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 2.02 [0.18, 22.39]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
In-transit metastases (first recurrence) at 8 years follow up (OR<1 favours narrow excision margin)								
Veronesi 1991	612	N/A	OR 1.01 [0.14, 7.19]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
(World Health Organisation (WHO) melanoma group)								
Regional nodal metastases at a mean follow up of 55 months (OR<1 favours narrow excision margin)								
Veronesi 1988 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 0.69 [0.34, 1.39]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Regional nodal metastases (first recurrence) at 8 years follow up (OR<1 favours narrow excision margin)								
Veronesi 1991 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 0.87 [0.47, 1.60]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Distant metastases at a mean follow up of 55 months (OR<1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Veronesi 1988 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 0.88 [0.31, 2.45]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Distant metastases (first recurrence) at 8 years follow up (OR<1 favours narrow excision margin)								
Veronesi 1991 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 1.24 [0.60, 2.55]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Any recurrence at a mean follow up of 55 months (OR<1 favours narrow excision margin)								
Veronesi 1988 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 0.89 [0.51, 1.56]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Any recurrence at 8 years follow up (OR<1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Veronesi 1991 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 1.13 [0.71, 1.78]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low

1. Study was at high risk of bias: A significant number of participants were excluded following randomisation (75/612 = 12%). While the majority of these were due to non-eligibility discovered following randomisation, 15 were due to a "mistake in treatment" and 1 due to "loss to follow up". This suggests a per protocol approach to analysis. In addition, neither participants nor assessors were blinded. A significant number were excluded, but these were due to not adhering to study protocol. Participants were unblinded. Outcome assessors do not appear to have been blinded to study arms. For per-protocol analysis, study was at moderate risk of bias.
2. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for odds ratios)

Overall survival

Table 12 Survival

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall survival at a median follow-up of 55 months (OR>1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Veronesi 1988 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 1.20 [0.51, 2.82]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Overall survival at 8 years (OR>1 favours narrow excision margin)								
Veronesi 1991 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 0.92 [0.55, 1.56]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
Overall survival at 12 years (OR>1 favours narrow excision margin)								
Cascinelli 1998 (World Health Organisation (WHO) melanoma group)	612	N/A	OR 1.20 [0.76, 1.90]	Very serious ¹	Not serious	N/A	Very Serious ²	Very low
1. Study was at high risk of bias: A significant number of participants were excluded following randomisation (75/612 = 12%). While the majority of these were due to non-eligibility discovered following randomisation, 15 were due to a "mistake in treatment" and 1 due to "loss to follow up". This suggests a per protocol approach to analysis.								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
addition, neither participants nor assessors were blinded. A significant number were excluded, but these were due to not adhering to study protocol. Participants were unblinded. Outcome assessors do not appear to have been blinded to study arms. For per-protocol analysis, study was at moderate risk of bias.								
2. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for odds ratios)								

2 cm excision vs 4 cm excision

Local, regional, and distant recurrence

Table 13 Recurrence

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall disease-free survival at 6.7 years (HR>1 favours narrow excision margin)								
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 1.01 (0.83–1.24) ³	Serious ⁴	Not serious	N/A	Not Serious	Moderate
Overall disease-free survival at 5 years (OR>1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Karakousis 1996 (Intergroup Melanoma Surgical Trial)	468	N/A	OR 0.75 [0.48, 1.16]	Serious ¹	Not serious	N/A	Serious ²	Low
Local recurrence after a median follow up time of 72 months (OR<1 favours narrow excision margin)								
Balch 1993 (Intergroup Melanoma Surgical Trial)	486	N/A	OR 0.33 [0.06, 1.63]	Serious ¹	Not serious	N/A	Very Serious ²	Very low
Local recurrence over follow-up (median 6.7 years) (HR<1 favours narrow excision margin)								
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 2.15 (0.97 to 4.77)	Serious ³	Not serious	N/A	Serious ⁴	Low
Local recurrence after a median follow-up time of 92 months (OR<1 favours narrow excision margin)								
Balch 1993 (Intergroup Melanoma Surgical Trial)	486	N/A	OR 0.81 [0.24, 2.69]	Serious ¹	Not serious	N/A	Very Serious ²	Very low
Local recurrence as a first recurrence with a median follow-up of 10 years and a range up to 16 years (OR<1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Balch 2001 (Intergroup Melanoma Surgical Trial)	468	N/A	OR 0.48 [0.04, 5.34]	Serious ¹	Not serious	N/A	Very Serious ²	Very low
Any local recurrence with a median follow-up of 10 years and a range up to 16 years (OR<1 favours narrow excision margin)								
Balch 2001 (Intergroup Melanoma Surgical Trial)	468	N/A	OR 0.80 [0.24, 2.66]	Serious ¹	Not serious	N/A	Very Serious ²	Very low
In-transit metastases after a median follow-up time of 72 months (OR<1 favours narrow excision margin)								
Balch 1993 (Intergroup Melanoma Surgical Trial)	486	N/A	OR 0.82 [0.25, 2.73]	Serious ¹	Not serious	N/A	Very Serious ²	Very low
Regional skin metastases over follow up (median 6.7 years) (HR<1 favours narrow excision margin)								
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 1.25 (0.63–2.46)	Serious ³	Not serious	N/A	Very Serious ²	Very low
Regional lymph node recurrence over follow-up (median 6.7 years) (HR<1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 0.88 (0.68 to 1.16)	Serious ³	Not serious	N/A	Serious ⁴	Low
Any loco-regional recurrence over follow up (median 6.7 years) (HR<1 favours narrow excision margin)								
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 1.00 (0.79 to 1.28)	Serious ³	Not serious	N/A	Very Serious ²	Very low
Distant metastases after a median follow up time of 72 months (OR<1 favours narrow excision margin)								
Balch 1993 (Intergroup Melanoma Surgical Trial)	486	N/A	OR 0.78 [0.43, 1.43]	Serious ¹	Not serious	N/A	Very Serious ²	Very low
Distant metastasis over follow up (median 6.7 years) (HR<1 favours narrow excision margin)								
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 0.71 (0.47 to 1.08)	Serious ³	Not serious	N/A	Serious ⁴	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<ol style="list-style-type: none"> 1. Study was at moderate risk of bias: The studies lacked detail about any protocol deviations or missing data. In addition, some outcomes were altered in one paper, but justification "according to the protocol, local recurrence was considered as one occurring within 2 cm from the surgical scar of the first definitive operation for the primary lesion (a patient with multiple in-transit metastases and a lesion within 2-cm of the scar was not counted as a local recurrence). This is a well accepted, clinically used, biologically arbitrary definition. However, it is obvious that a recurrent lesion near the primary site may be variously classified as local recurrence or in-transit metastases according to the definition of local recurrence. To avoid any effect the arbitrariness of the definition may have had in estimating the rates of local recurrence, in the forest analysis, in addition to the local recurrence rates, the rates of in-transit metastases, combined rates of local and in-transit recurrences, and rates of distant metastases were compared between the two surgical margin groups." 2. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for odds ratios) 3. Study was at moderate risk of bias: Lack of blinding at any point and some minor protocol deviations, as well as a greater proportion of patients in the 2cm group undergoing sentinel node biopsy, however these were unlikely to impact the results of the trial. 4. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for odds ratios or hazard ratios) 								

Overall survival and melanoma-specific survival

Table 14 Survival

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall survival at a median follow-up of 10 years (OR>1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Balch 2001 (Intergroup Melanoma Surgical Trial)	468	N/A	OR 0.70 [0.47, 1.07]	Serious ¹	Not serious	N/A	Serious ²	Low
Overall survival at a median follow-up of 6.7 years (HR>1 favours narrow excision margin)								
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	aHR 1.11 (0.90–1.37) ³	Serious ⁴	Not serious	N/A	Serious ²	Low
Overall survival at 5 years (OR>1 favours narrow excision margin)								
Balch 2001 (Intergroup Melanoma Surgical Trial)	468	N/A	OR 0.75 [0.47, 1.18]	Serious ¹	Not serious	N/A	Serious ²	Low
Overall survival at 5 years (OR>1 favours narrow excision margin)								
Karakousis 1996 (Intergroup Melanoma Surgical Trial)	468	N/A	OR 0.70 [0.45, 1.10]	Serious ¹	Not serious	N/A	Serious ²	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Rate of death over follow up (median 19·6 years) (HR<1 favours narrow excision margin)								
Utjes 2019 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 0·98 (0·83–1·14)	Serious ⁴	Not serious	N/A	Not Serious	Moderate
Melanoma-specific rate of death over follow up (median 19·6 years) (HR<1 favours narrow excision margin)								
Utjes 2019 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 0·95 (0·78–1·16)	Serious ⁴	Not serious	N/A	Serious ²	Low
Rate of death over follow up (median 19·6 years) (HR<1 favours narrow excision margin)								
Utjes 2019 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	aHR 1·02 (0·87–1·19) ⁵	Serious ⁴	Not serious	N/A	Not Serious	Moderate
Melanoma-specific rate of death over follow up (median 19·6 years) (HR<1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Utjes 2019 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	aHR 0.99 (0.81–1.20) ⁴	Serious ⁴	Not serious	N/A	Not Serious	Moderate
Rate of death over follow up (median 6.7 years) (HR<1 favours narrow excision margin)								
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 1.05 (0.85–1.29)	Serious ⁴	Not serious	N/A	Serious ²	Moderate
Melanoma-specific rate of death over follow up (median 6.7 years) (HR<1 favours narrow excision margin)								
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	HR 0.99 (0.78–1.26)	Serious ⁴	Not serious	N/A	Very Serious ⁶	Very Low
<p>1. Study was at moderate risk of bias: The studies lacked detail about any protocol deviations or missing data. In addition, some outcomes were altered in one paper, but with justification "according to the protocol, local recurrence was considered as one occurring within 2 cm from the surgical scar of the first definitive operation for the primary lesion (a patient with multiple in-transit metastases and a lesion within 2-cm of the scar was not counted as a local recurrence). This is a well-accepted, clinically used, biologically arbitrary definition. However, it is obvious that a recurrent lesion near the primary site may be variously classified as local recurrence or in-transit metastasis according to the definition of local recurrence. To avoid any effect the arbitrariness of the definition may have had in estimating the rates of local recurrence, in the fo</p>								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
analysis, in addition to the local recurrence rates, the rates of in-transit metastases, combined rates of local and in-transit recurrences, and rates of distant metastases compared between the two surgical margin groups.")								
2. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for odds ratios or hazard ratios).								
3. Adjusted for age, sex, site, thickness, and ulceration								
4. Study was at moderate risk of bias: Lack of blinding at any point and some minor protocol deviations, as well as a greater proportion of patients in the 2cm group undergoing sentinel node biopsy, however these were unlikely to impact the results of the trial.								
5. Adjusted for age and sex.								
6. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for hazard ratios).								

Surgical adverse events and length of hospital stay

Table 15 Surgical adverse events and length of hospital stay

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Need for a skin graft following intervention (OR<1 favours narrow excision group)								
Balch 1993 (Intergroup Melanoma Surgical Trial)	486	N/A	OR 0.20 [0.10, 0.40]	Serious ¹	Not serious	N/A	Not Serious	Moderate
Need for a skin graft following intervention (OR<1 favours narrow excision group)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Gillgren 2011 (Swedish Melanoma Group/ Danish Melanoma Group)	936	N/A	OR 0.16 [0.11, 0.22]	Serious ⁴	Not serious	N/A	Not Serious	Moderate
Length of hospital stay following intervention (MD<0 favours narrow excision group)								
Balch 1993 (Intergroup Melanoma Surgical Trial)	486	N/A	MD -1.80 [-2.66, -0.94]	Serious ¹	Not serious	N/A	Serious ²	Very Low
Wound infection rate following intervention (OR<1 favours narrow excision group)								
Balch 1993 (Intergroup Melanoma Surgical Trial)	486	N/A	OR 1.18 [0.52, 2.69]	Serious ¹	Not serious	N/A	Very Serious ³	Very Low
Wound dehiscence rates following intervention (OR<1 favours narrow excision group)								
Balch 1993 (Intergroup Melanoma Surgical Trial)	486	N/A	OR 1.10 [0.46, 2.63]	Serious ¹	Not serious	N/A	Very Serious ³	Very Low
“problems with the scar” at 4 or 15 months following randomisation (OR<1 favours narrow excision group)								
Bergenmar 2010 (?Swedish)	144	Subgroup study of	OR 0.64 [0.28, 1.46]	Very Serious ⁵	Not serious	N/A	Very Serious ³	Very Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Quality
				Indirectness	Inconsistency	Imprecision	
Melanoma Group)		participants who were sent a series of QoL-related questionnaires					

1. Study was at moderate risk of bias: The studies lacked detail about any protocol deviations or missing data. In addition, some outcomes were altered in one paper, but with justification "according to the protocol, local recurrence was considered as one occurring within 2 cm from the surgical scar of the first definitive operation for the primary lesion (a patient with multiple in-transit metastases and a lesion within 2-cm of the scar was not counted as a local recurrence). This is a well accepted, clinically used, but biologically arbitrary definition. However, it is obvious that a recurrent lesion near the primary site may be variously classified as local recurrence or in-transit metastasis according to the definition of local recurrence. To avoid any effect the arbitrariness of the definition may have had in estimating the rates of local recurrence, in the forest plot analysis, in addition to the local recurrence rates, the rates of in-transit metastases, combined rates of local and in-transit recurrences, and rates of distant metastases were compared between the two surgical margin groups.")
2. Study was marked down one level for imprecision as confidence intervals crossed one line of minimum important difference (defined as 0.5*SD in the control group=)
3. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for odds ratios).
4. Study was at moderate risk of bias: Lack of blinding at any point and some minor protocol deviations, as well as a greater proportion of patients in the 2cm group undergoing a sentinel node biopsy, however these were unlikely to impact the results of the trial.
5. Study was downgraded two levels for very serious risk of bias: The first assessment was done before randomisation. Unclear how randomisation was performed. Unclear if allocation concealment. Very few baseline characteristics were reported with which to assess the success of randomisation. Unclear if any deviations from intended intervention. By the end of follow up the amount of missing data was significant (88%). It is unclear how the extent of missing data varied between arms. Following randomisation, 17 patients were not informed about the health-related QoL study and hence not included. Following intervention, 28 were excluded during the study because of: recurrence of melanoma (n = 20) as one would expect a recurrence to adversely affect both quality of life and to increase emotional distress; a new diagnosis of cancer (n = 3); inclusion in another clinical trial (n = 2); death (n = 2); and one patient who had moved outside the catchment area. Insufficient justification or detail for the methods provided and protocol is not cited.

Quality of life scores**Table 16 quality of life scores**

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Quality	
				Indirectness	Inconsistency	Imprecision		
Physical functioning score at 3 months post-randomisation, measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 1.63 [-1.53, 4.79]	Very Serious ¹	Not serious	N/A	Serious ²	Very Low
Physical functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -1.35 [-4.80, 2.10]	Very Serious ¹	Not serious	N/A	Serious ³	Very Low
Role functioning score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Imprecision	Quality
				Indirectness	Inconsistency			
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 3.29 [-5.00, 11.58]	Very Serious ¹	Not serious	N/A	Not Serious ⁴	Low
Role functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -2.49 [-7.09, 2.11]	Very Serious ¹	Not serious	N/A	Serious ⁵	Very Low
Emotional functioning score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of	MD 3.73 [0.89, 6.57]	Very Serious ¹	Not serious	N/A	Not Serious ⁶	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Imprecision	Quality
				Indirectness	Inconsistency			
		QoL-related questionnaires						
Emotional functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 1.54 [-4.29, 7.37]	Very Serious ¹	Not serious	N/A	Not Serious ⁷	Low
Cognitive functioning score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 2.01 [-2.87, 6.89]	Very Serious ¹	Not serious	N/A	Not Serious ⁸	Low
Cognitive functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Imprecision	Quality
				Indirectness	Inconsistency			
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 0.18 [-4.58, 4.94]	Very Serious ¹	Not serious	N/A	Not Serious ⁹	Low
Social functioning score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 3.84 [-1.78, 9.46]	Very Serious ¹	Not serious	N/A	Serious ¹⁰	Very Low
Social functioning score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of	MD 3.07 [-1.84, 7.98]	Very Serious ¹	Not serious	N/A	Serious ¹¹	Very Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		QoL-related questionnaires						
Global quality of life at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 4.87 [-1.81, 11.55]	Very Serious ¹	Not serious	N/A	Serious ¹²	Very Low
Global quality of life at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 2.96 [-3.92, 9.84]	Very Serious ¹	Not serious	N/A	Serious ¹²	Very Low
Fatigue score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -6.19 [-12.47, 0.09]	Very Serious ¹	Not serious	N/A	Serious ¹⁴	Very Low
Fatigue score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -0.26 [-6.77, 6.25]	Very Serious ¹	Not serious	N/A	Not Serious ¹⁵	Low
Pain score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of	MD -1.98 [-7.97, 4.01]	Very Serious ¹	Not serious	N/A	Not Serious ¹⁶	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		QoL-related questionnaires						
Pain score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 2.60 [-3.47, 8.67]	Very Serious ¹	Not serious	N/A	Serious ¹⁷	Very Low
Insomnia score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -8.34 [-15.91, -0.77]	Very Serious ¹	Not serious	N/A	Serious ¹⁸	Very Low
Insomnia score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD 2.57 [-5.32, 10.46]	Very Serious ¹	Not serious	N/A	Not Serious ¹⁹	Low
Financial difficulties score at 3 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -2.49 [-9.23, 4.25]	Very Serious ¹	Not serious	N/A	Not Serious ²⁰	Low
Financial difficulties score at 15 months post-randomisation, measured using the EORTC QLQ-C30 (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of	MD -0.29 [-4.14, 3.56]	Very Serious ¹	Not serious	N/A	Not Serious ²¹	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias			Imprecision	Quality
				Indirectness	Inconsistency			
		QoL-related questionnaires						
Clinical anxiety score at 3 months post randomisation, measured using the HAD-A questionnaire (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -0.10 [-1.58, 1.38]	Very Serious ¹	Not serious	N/A	Not Serious ²²	Low
Clinical anxiety score at 15 months post randomisation, measured using the HAD-A questionnaire (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -0.56 [-2.24, 1.12]	Very Serious ¹	Not serious	N/A	Serious ²³	Very Low
Clinical depression score at 3 months post randomisation, measured using the HAD-D questionnaire (higher score = better functioning)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -0.36 [-1.38, 0.66]	Very Serious ¹	Not serious	N/A	Serious ²⁴	Very Low
Clinical depression score at 15 months post randomisation, measured using the HAD-D questionnaire (higher score = better functioning)								
Bergenmar 2010 (?Swedish Melanoma Group)	144	Subgroup study of participants who were sent a series of QoL-related questionnaires	MD -0.17 [-1.39, 1.05]	Very Serious ¹	Not serious	N/A	Not Serious ²⁵	Low
<p>1. Study was downgraded two levels for very serious risk of bias: The first assessment was done before randomisation. Unclear how randomisation was performed. Unclear how allocation concealment. Very few baseline characteristics were reported with which to assess the success of randomisation. Unclear if any deviations from intended intervention. By the end of follow up the amount of missing data was significant (88%). It is unclear how the extent of missing data varied between arms. Following randomisation, 17 patients were not informed about the health-related QoL study and hence not included. Following intervention, 28 were excluded during the study because of: recurrence of melanoma (n = 20) as one would expect a recurrence to adversely affect both quality of life and to increase emotional distress; a new diagnosis of cancer (n = 3); inclusion in another clinical trial (n = 2); death (n = 2); and one patient who had moved outside the catchment area. Insufficient justification or detail for methods provided and protocol is not cited. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 4.53)</p>								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<ol style="list-style-type: none"> 2. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 3.78) 3. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 12.64) 4. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 4.26) 5. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 7.00) 6. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 8.75) 7. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 7.54) 8. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 7.12) 9. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 8.15) 10. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 7.97) 11. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 9.37) 12. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 9.52) 13. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 9.75) 14. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 8.26) 15. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 8.38) 16. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 6.34) 17. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 12.11) 18. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 10.67) 19. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 10.13) 20. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 4.38) 								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
21. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 1.92) 22. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 2.21) 23. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 1.98) 24. Study did not a cross line of minimum important difference (0.5* the standard deviation in the control arm = 1.64) 25. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimum important difference (0.5* the standard deviation in the control arm = 1.29)								

2 cm vs ≥5 cm

Overall survival and melanoma-specific survival

Table 17 Survival

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall survival at 10 years of follow up (OR>1 favours narrow excision group)								
Khayat 2003 (Large)	326	N/A	OR 1.08 [0.57, 2.04]	Very Serious ¹	Not Serious	N/A	Very Serious ²	Very Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
European Multicentric Phase III Study)								
Death at 20 years of follow up (OR<1 favours narrow excision group)								
Khayat 2003 (Large European Multicentric Phase III Study)	326	N/A	OR 1.16 [0.67, 2.03]	Very Serious ¹	Not Serious	N/A	Very Serious ²	Very Low
Overall survival at a median follow-up of 11 years [range 7 to 17 years] (HR <1 favours narrow excision margin)								
Cohn-Cedermark 2000 (Swedish Melanoma Study Group)	989	N/A	HR 0.96 (0.75–1.24)	Serious ⁴	Not serious	N/A	Serious ³	Low
Any death at a median follow-up of 5.8 years (HR <1 favours narrow excision margin)								
Ringborg 1996 (Swedish Melanoma Study Group)	769	N/A	HR 1.00 (0.68-1.47)	Serious ⁴	Not serious	N/A	Very Serious ²	Very Low
Melanoma-specific survival (from death) over follow up (median 11 years) (HR<1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Cohn-Cedermark 2000 (Swedish Melanoma Study Group)	989	N/A	HR 1.22 (0.88–1.69)	Serious ⁴	Not serious	N/A	Serious ³	Low
Melanoma specific death at a median follow-up of 5.8 years (HR <1 favours narrow excision margin)								
Ringborg 1996 (Swedish Melanoma Study Group)	769	N/A	HR 1.31 (0.79-2.15)	Serious ⁴	Not serious	N/A	Very Serious ²	Very Low
<ol style="list-style-type: none"> 1. Study was downgraded two levels for being high risk of bias: Non-blinded assessments. Unclear approach to analysis (e.g. intention to treat). Unclear approach to randomisation or allocation concealment. Large attrition/missing data at 20 years follow up. 2. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for hazard or odds ratio). 3. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for hazard or odds ratio). 4. Study was at moderate risk of bias (or high risk of bias for per-protocol analysis): The median resection margin in the narrow excision group was 2 cm (range, 0.2–5.0 cm) and it was 5 cm (range, 0.2–10.0 cm) in the wide excision group (mean resection margin, 2.1 cm vs. 4.6 cm). Seventy-five percent of the patients in each treatment group were treated with the exact allocated excision margin." However, it is unclear whether deviations from the intended interventions were as a result of the experimental design. Intention to treat analysis was used. Deviations appeared to be balanced between groups. Separate analyses also were done excluding the ineligible patients, leading to identical conclusions. Patients were ineligible for not meeting inclusion criteria following randomisation. Outcome assessors were unblinded, and for some outcomes (local recurrence, regional cutaneous metastasis, and regional lymph node metastasis, it was unclear which definitions were used 								

Local, regional, and distant recurrence**Table 18 Recurrence**

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
No tumour recurrence at 20 years of follow up (OR>1 favours narrow excision group)								
Khayat 2003 (Large European Multicentric Phase III Study)	326	N/A	OR 1.11 [0.72, 1.73]	Very Serious ¹	Not Serious	N/A	Very Serious ²	Very Low
Disease-free survival at 10 years of follow up (OR>1 favours narrow excision group)								
Khayat 2003 (Large European Multicentric Phase III Study)	326	N/A	OR 1.17 [0.64, 2.11]	Very Serious ¹	Not Serious	N/A	Very Serious ²	Very Low
Tumour recurrence at 20 years of follow up (OR<1 favours narrow excision group)								
Khayat 2003 (Large European Multicentric Phase III Study)	326	N/A	OR 0.63 [0.35, 1.14]	Very Serious ¹	Not Serious	N/A	Serious ³	Very Low
Local recurrence at 20 years of follow up (OR<1 favours narrow excision group)								
Khayat 2003 (Large	326	N/A	OR 0.25 [0.03, 2.28]	Very Serious ¹	Not Serious	N/A	Very Serious ²	Very Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
European Multicentric Phase III Study)								
Distant recurrence at 20 years of follow up (OR<1 favours narrow excision group)								
Khayat 2003 (Large European Multicentric Phase III Study)	326	N/A	OR 0.39 [0.12, 1.29]	Very Serious ¹	Not Serious	N/A	Very Serious ²	Very Low
Regional lymph node recurrence at 20 years of follow up (OR<1 favours narrow excision group)								
Khayat 2003 (Large European Multicentric Phase III Study)	326	N/A	OR 1.23 [0.53, 2.83]	Very Serious ¹	Not Serious	N/A	Very Serious ²	Very Low
Locoregional recurrence with a median follow-up of 8 years [range 0 to 17 years] (HR<1 favours narrow excision margin) defined as local recurrence, regional skin metastases, or regional lymph node metastases								
Cohn-Cedermark 2000 (Swedish Melanoma Study Group)	989	N/A	HR 1.24 (0.88–1.75)	Serious ⁴	Not serious	N/A	Serious ²	Low
Distant metastases with a median follow-up of 8 years [range 0 to 17 years] (HR<1 favours narrow excision margin)								

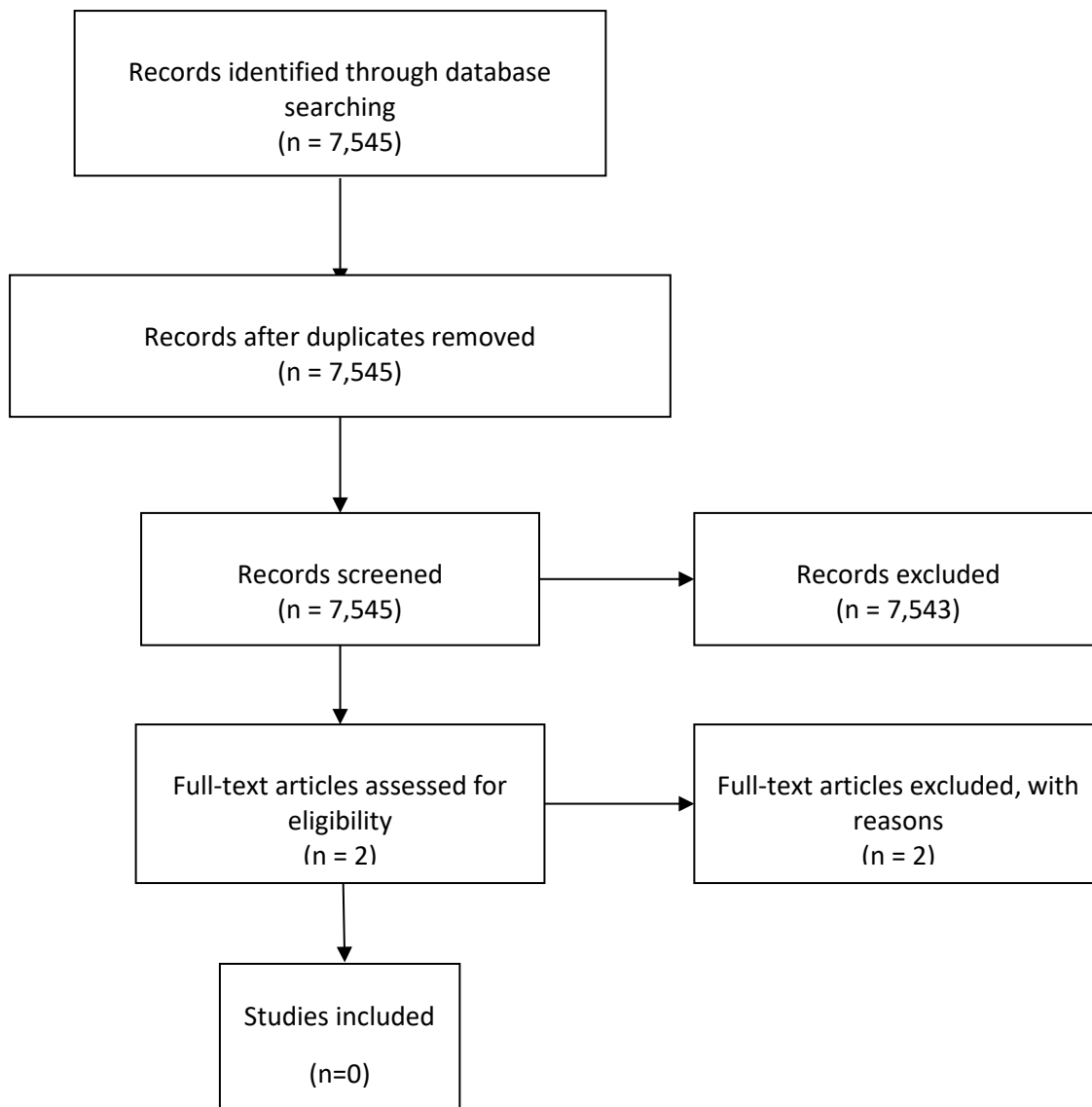
Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Cohn-Cedermark 2000 (Swedish Melanoma Study Group)	989	N/A	HR 0.76 (0.45–1.28)	Serious ⁴	Not serious	N/A	Very Serious ³	Very Low
New primary melanoma with a median follow-up of 8 years [range 0 to 17 years] (HR<1 favours narrow excision margin)								
Cohn-Cedermark 2000 (Swedish Melanoma Study Group)	989	N/A	HR 1.42 (0.59–3.40)	Serious ⁴	Not serious	N/A	Very Serious ³	Very Low
Any event with a median follow-up of 8 years [range 0 to 17 years] (HR<1 favours narrow excision margin) defined as locoregional recurrence, distant metastasis, primary melanoma, or intercurrent death								
Cohn-Cedermark 2000 (Swedish Melanoma Study Group)	989	N/A	HR 0.75 (0.43–1.30)	Serious ⁴	Not serious	N/A	Very Serious ³	Very Low
Local recurrence at a median follow up of 4 years (HR<1 favours narrow excision margin)								
Ringborg 1996	769	N/A	HR 0.87 (0.19-3.91)	Serious ⁴	Not serious	N/A	Very Serious ³	Very Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
(Swedish Melanoma Study Group)								
Regional cutaneous metastasis at a median follow up of 4 years (HR<1 favours narrow excision margin)								
Ringborg 1996 (Swedish Melanoma Study Group)	769	N/A	HR 1.44 (0.50-4.17)	Serious ⁴	Not serious	N/A	Very Serious ³	Very Low
Regional lymph node metastasis at a median follow up of 4 years (HR<1 favours narrow excision margin)								
Ringborg 1996 (Swedish Melanoma Study Group)	769	N/A	HR 1.56 (0.99-2.45)	Serious ⁴	Not serious	N/A	Serious ³	Low
Distant metastases at a median follow up of 4 years (HR<1 favours narrow excision margin)								
Ringborg 1996 (Swedish Melanoma Study Group)	769	N/A	HR 1.22 (0.77-1.93)	Serious ⁴	Not serious	N/A	Very Serious ²	Very Low
Any recurrence at a median follow up of 4 years (HR<1 favours narrow excision margin)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Ringborg 1996 (Swedish Melanoma Study Group)	769	N/A	HR 1.07 (0.78-1.46)	Serious ⁴	Not serious	N/A	Very Serious ²	Very Low

1. Study was downgraded two levels for being high risk of bias: Non-blinded assessments. Unclear approach to analysis (e.g. intention to treat). Unclear approach to randomisation or allocation concealment. Large attrition/missing data at 20 years follow up
2. Study was marked down two levels for imprecision as the confidential intervals crossed two lines of minimal important difference (0.8 and 1.25 for hazard or odds ratio)
3. Study was marked down one level for imprecision as the confidential intervals crossed one line of minimal important difference (0.8 and 1.25 for hazard or odds ratio)
4. Study was at moderate risk of bias (or high risk of bias for per-protocol analysis): The median resection margin in the narrow excision group was 2 cm (range, 0.2–5.0 cm) and it was 5 cm (range, 0.2–10.0 cm) in the wide excision group (mean resection margin, 2.1 cm vs. 4.6 cm). Seventy-five percent of the patients in each treatment group were treated with the exact allocated excision margin." However, it is unclear whether deviations from the intended interventions were as a result of the experimental design. Intention to treat analysis was used. Deviations appeared to be balanced between groups. Separate analyses also were done excluding the ineligible patients, leading to identical conclusions. Patients were ineligible for not meeting inclusion criteria following randomisation. Outcome assessors were unblinded, and for some outcomes (local recurrence, regional cutaneous metastasis, and regional lymph node metastasis, it was unclear which definitions were used

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was found for this review question.

Appendix I – Health economic model

No original health economic modelling was completed for this review question.

Appendix J – Excluded studies

Clinical studies

Study	Code [Reason]
(2020) 2-cm versus 4-cm surgical excision margin for thick (>2 mm) primary malignant melanoma: long-term follow-up of a multicenter randomized trial. <i>European journal of surgical oncology</i> 46(2): e15-e16	- Conference abstract.
Alonso-Rochi, RJV, Blakely, AM, Baird, G et al. (2017) Effects of histopathologic margin measurements on recurrence for invasive melanomas. <i>Annals of surgical oncology</i> 24(1): S136	- non-randomised
Angeles, C V; Wong, S L; Karakousis, G (2020) ASO Author Reflections: Surgical Margins for Melanoma-What's Next?. <i>Annals of surgical oncology</i> 27(1): 13-14	- Review
Angeles, C V; Wong, S L; Karakousis, G (2020) The Landmark Series: Randomized Trials Examining Surgical Margins for Cutaneous Melanoma. <i>Annals of surgical oncology</i> 27(1): 3-12	- Review
Anonymous. (2011) Erratum: 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre	- Erratum

Study	Code [Reason]
trial (The Lancet (2011) 378(9803) (1635-1642) (S0140673611615468) (10.1016/S0140-6736(11)61546-8)). The Lancet 378(9803): 1626	
Banzet P, et al. (1993) Wide versus narrow surgical excision in thin (<2mm) stage 1 primary cutaneous melanoma: long term results of a French multicentre prospective randomized trial on 319 patients. Proceedings of the American Society of Clinical Oncology March;12:387.	- Conference abstract
Bergenmar, M., et al (2008) Health related quality of life in patients with malignant melanoma included in a randomized study of resection margins. Pigment Cell & Melanoma Research, 21: 333.	- Conference abstract
Bergenmar, M., Mansson-Brahme, E., Hansson, J. et al. (2010) Surgical resection margins do not influence health related quality of life or emotional distress in patients with cutaneous melanoma: results of a prospective randomised trial. Scandinavian journal of plastic and reconstructive surgery and hand surgery / Nordisk plastikkirurgisk forening [and] Nordisk klubb for handkirurgi 44(3): 146-155	- Duplicate reference
Breuninger, Helmut, Eigentler, Thomas, Hafner, Hans-Martin et al. (2019) Local surgical treatment of cutaneous squamous cell carcinoma: deficits and controversies in the literature. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG 17(10): 999-1004	- Review - Guidelines

Study	Code [Reason]
Chae, Y-S, Lee, J-Y, Lee, J-W et al. (2020) Survival of oral mucosal melanoma according to treatment, tumour resection margin, and metastases. <i>The British journal of oral & maxillofacial surgery</i> 58(9): 1097-1102	- non-randomised
Chatzistefanou, Ioannis, Kolokythas, Antonia, Vahsevanos, Konstantinos et al. (2016) Primary mucosal melanoma of the oral cavity: current therapy and future directions. <i>Oral surgery, oral medicine, oral pathology and oral radiology</i> 122(1): 17-27	- Review
Coit, Daniel and Ariyan, Charlotte (2018) MelMART Trial: It's Now or Never. <i>Annals of surgical oncology</i> 25(9): 2493-2495	- Review
Costa Svedman, F, Spanopoulos, D, Taylor, A et al. (2017) Surgical outcomes in patients with cutaneous malignant melanoma in Europe - a systematic literature review. <i>Journal of the European Academy of Dermatology and Venereology</i> : JEADV 31(4): 603-615	- Systematic review (checked for citations)
Hanna, S.; Lo, S.N.; Saw, R.P. (2021) Surgical excision margins in primary cutaneous melanoma: A systematic review and meta-analysis. <i>European Journal of Surgical Oncology</i>	- Systematic review (checked for citations)
Hunger, Robert E, Angermeier, Sarina, Seyed Jafari, S Morteza et al. (2015) A retrospective study of 1- versus 2-cm excision margins for cutaneous malignant melanomas thicker than 2 mm. <i>Journal of the American Academy of Dermatology</i> 72(6): 1054-9	- non-randomised

Study	Code [Reason]
Liu, Annie, Botkin, Alexis, Murray, Christian et al. (2018) Treatment for Lentigo Maligna of the Head and Neck: Survey of Practices in Ontario, Canada. <i>Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]</i> 44(7): 918-923	- non-randomised - non-controlled study
Lo, MC, Turner, D, Henderson, M et al. (2017) Melanoma margins trial: early effects of narrow excision margins for melanoma on quality of life, a feasibility study. <i>Annals of surgical oncology</i> 24(1): S135-S136	- Conference abstract.
Lo, Michelle Chin, Heaton, Martin J, Snelling, Andrew et al. (2020) Reconstructive burden and financial implications of wider excision margins for invasive primary cutaneous melanoma. <i>Journal of plastic, reconstructive & aesthetic surgery : JPRAS</i> 73(2): 313-318	- non-randomised
Moncrieff, M, Saw, R, Spillane, A et al. (2016) Preliminary feasibility data from the melanoma margins trial (MelMarT) pilot study: australian and New Zealand melanoma trials group (ANZMTG) study 03.12. <i>Annals of surgical oncology</i> . 23(1suppl1): 122	- Conference abstract.
Moncrieff, MD, Gyorki, D, Saw, RPM et al. (2020) Melanoma Margin Trial (MelMarT-II): a phase III, multi-centre, multi-national randomised control trial investigating 1 cm v 2 cm wide excision margins for primary cutaneous melanoma. <i>Asia-Pacific journal of clinical oncology</i> 16(suppl8): 122	- Conference abstract.

Study	Code [Reason]
Nakamura, Yasuhiro, Ohara, Kuniaki, Kishi, Akiko et al. (2015) Effects of non-amputative wide local excision on the local control and prognosis of in situ and invasive subungual melanoma. <i>The Journal of dermatology</i> 42(9): 861-6	<ul style="list-style-type: none"> - non-randomised - non-controlled study
NCT02385214 (2015) MelmarT Melanoma Margins Trial Investigating 1cm v 2cm Wide Excision Margins for Primary Cutaneous Melanoma. https://clinicaltrials.gov/show/NCT02385214	<ul style="list-style-type: none"> - Trial registration
NCT03034395 (2017) Study of 1cm Versus 2cm Margins for the Surgical Treatment of cT2N0M0 Melanoma. https://clinicaltrials.gov/show/NCT03034395	<ul style="list-style-type: none"> - Trial registration
NCT03638492 (2018) Trial of Surgical Excision Margins in Thick Primary Melanoma - 2. https://clinicaltrials.gov/show/NCT03638492	<ul style="list-style-type: none"> - Trial registration
Phan, Kevin, Oh, Lawrence J, Goyal, Sourabh et al. (2020) Recurrence rates following surgical excision of periocular basal cell carcinomas: systematic review and meta-analysis. <i>The Journal of dermatological treatment</i> 31(6): 597-601	<ul style="list-style-type: none"> - Systematic review (checked for citations)
Shelton, Megan E and Adamson, Adewole S (2019) Review and Update on Evidence-Based Surgical Treatment Recommendations for Nonmelanoma Skin Cancer. <i>Dermatologic clinics</i> 37(4): 425-433	<ul style="list-style-type: none"> - Guidelines

Study	Code [Reason]
Sladden, Michael J, Nieweg, Omgo E, Howle, Julie et al. (2018) Updated evidence-based clinical practice guidelines for the diagnosis and management of melanoma: definitive excision margins for primary cutaneous melanoma. <i>The Medical journal of Australia</i> 208(3): 137-142	- Guidelines
Tzellos, Thrasivoulos, Kyrgidis, Athanassios, Mocellin, Simone et al. (2014) Interventions for melanoma in situ, including lentigo maligna. <i>The Cochrane database of systematic reviews</i> : cd010308	- Systematic review (checked for citations)
Wheatley, Keith, Wilson, Jayne S, Gaunt, Piers et al. (2016) Surgical excision margins in primary cutaneous melanoma: A meta-analysis and Bayesian probability evaluation. <i>Cancer treatment reviews</i> 42: 73-81	- Systematic review (checked for citations)
Wright, F C, Souter, L H, Kellett, S et al. (2019) Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline. <i>Current oncology (Toronto, Ont.)</i> 26(4): e541-e550	- Guidelines
Yan, Lu, Sun, Ledong, Guan, Zhiguang et al. (2020) Analysis of cutaneous Merkel cell carcinoma outcomes after different surgical interventions. <i>Journal of the American Academy of Dermatology</i> 82(6): 1422-1434	- non-randomised

Economic Studies

Study	Code [Reason]
Duncan, James Robert; Daugherty, Andrew; Elston, Carly; et al. (2021) Cost efficacy of wide local excision of pT1a melanoma in office versus operating room settings. Journal of the American Academy of Dermatology	- Editorial only, Research letter
Stoffels J, Dissemond J, Körber A et al. (2011) Reliability and cost-effectiveness of sentinel lymph node excision under local anaesthesia versus general anaesthesia for malignant melanoma: a retrospective analysis in 300 patients with malignant melanoma AJCC Stages I and II. Journal of the European Academy of Dermatology and Venereology 25(3) 306-310	- Not an economic evaluation.

Appendix K – Research recommendations – full details

1.1 *Histological margins*

Research recommendation 1 (histological margins)

1. What is the optimal histological margin to achieve following excision of stage 0 melanoma?

Why this is important

There is on-going research into the optimal clinical excisional margins and a growing consensus (and practice) towards thinner excisional margins. However, there remains uncertainty regarding what size histological margins are adequate following excision, particularly in stage 0 disease, to ensure no residual disease.

Rationale for research recommendation 1

Importance to 'patients' or the population	Identifying optimal histological margins will help to ensure quality and minimise variation between practices. This will allow people with in-site (stage 0) melanomas to have the best chances of being disease free following excision.
Relevance to NICE guidance	Current NICE guidance recommends discussing further management with the multidisciplinary team is an adequate histological margin is not achieved. Although the committee advised that a margin of 4mm may be most appropriate there was no evidence to justify this and therefore guidance in this area could not be given.
Relevance to the NHS	Recommendations in this area would help to reduce variance between practice and provide guidance in an area of uncertainty.
National priorities	Moderate

Current evidence base	No evidence
Equality considerations	None known

Modified PICO table

Population	People with a diagnosis of stage 0 undergoing surgical excision
Intervention (index test)	Surgical excision with aim of achieving following histological margin: <ul style="list-style-type: none"> • 1mm • 2mm • 3mm • 4mm • 5mm • 6mm • 7mm • 8mm • 9mm • 10mm
Comparator (reference standard)	Interventions compared to each other
Outcome	Disease recurrence Mortality Quality of life
Study design	RCT
Timeframe	Short-long term
Additional information	None