
Proceedings Paper:
Hayes, AJ, Maynard, L, A'Hern, R et al. (7 more authors) (2015) 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. Annual Meeting of the American-Society-of-Clinical-Oncology, 29 May - 02 Jun 2015, Chicago, IL, USA. American Society of Clinical Oncology .

Long term follow-up of survival in a randomised trial of wide or narrow excision margins in high risk primary melanoma

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Abstract

Background In the past there has been controversy concerning the necessary margin of excision for cutaneous melanomas greater than 2mm in thickness. Our previous report of a randomised trial of 1cm versus 3cm excision margins for this high risk group showed that narrow margins were associated with an increased rate of loco-regional relapse but there was no statistically significant difference in overall survival at a median follow-up of 5 years. We now report long term survival analysis of that trial.

Methods Patients from the UK and Poland with single primary localised cutaneous melanoma greater than 2mm in Breslow thickness were randomised 1:1 to a 1cm or 3cm excision margin. This analysis focusses on overall survival and melanoma-specific survival endpoints in the intention-to-treat population.

Findings Between 1993 and 2001, 453 patients were randomised to receive a 1cm excision and 447 were randomised to receive a 3cm excision. At a median follow-up of 106 months (IQR 76-135 months), a total of 494 patients have died with 359 of these deaths attributed to melanoma. There were 194 deaths attributed to melanoma in the 1cm group compared with 165 in the 3cm group (hazard ratio 1·24; 95% CI 1·00-1·52; P=0·047). While there was a higher number of deaths overall in the 1cm group compared to the 3cm group (253 versus 241) no statistically significant difference in overall survival was observed (hazard ratio 1·14: 95% CI 0·96-1·36, P=0·143).

Interpretation With longer follow-up, we observe a significant increase in melanoma-specific mortality in the narrow margins group, but no significant overall excess of deaths.

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.

Key Words

Melanoma, Surgery, Excision, Margins

Presented as an Oral Presentation at the 2015 Annual Meeting of the American Society of Clinical Oncology, May 30th 2015. Chicago, Illinois

Introduction

The risk of metastatic spread from malignant melanoma is estimated on the basis of histopathological features: the Breslow thickness, mitotic rate, and the presence of microscopic ulceration.[1,2] Whether the surgical margins that are taken around the primary tumour influence metastatic spread is unclear, despite having been the subject of a number of randomised clinical trials.[3–7] Historically, wide surgical margins were taken around primary melanomas in an attempt to excise the primary tumour but also to encompass local micro-metastatic disease in the vicinity of the tumour.[8,9] In all the previously reported randomised trials comparing wide (3-5cm) versus narrow (1-2cm) margins no significant difference in overall survival between test groups has been reported. As regards melanoma-specific survival, while no trial has demonstrated a statistically significant differential risk, there has been a suggestion from two trials[3,4] and in the previous report of this trial[10] that there might be a detrimental effect of narrow margins on melanoma survival. A Swedish Melanoma Study Group trial[3] randomised to either a 2cm or a 5cm excision margin for trunk and extremity melanomas with Breslow thickness between 0·8mm to 2mm (median Breslow thickness 1·2mm) and reported a hazard ratio for melanoma deaths for narrow margins compared with wide margins of 1·22 (95% CI, 0·88 to 1·69; P=0·24) with a median follow-up of 11 years. The Intergroup Melanoma Surgical Trial[4] randomised to either a 2cm or 4cm excision for trunk and extremity melanomas with Breslow thickness between 1mm and 4mm (median Breslow thickness 1·96mm) and reported a non-significant difference (P=0·07) in 10 year disease-specific survival of 70% for the 2cm group and a 77% for the 4cm group. However the second Swedish Melanoma Study Group trial[6] that randomised patients with melanomas greater than 2 mm thick (median Breslow thickness 3·1mm) to either a 2cm or a 4cm excision showed no difference in melanoma deaths in the two groups (HR 0·99; 95% CI 0·78-1·26; p=0·95).

In 2004 with a median 5 year follow-up in a trial of 1cm margins versus 3cm margins for melanomas 2mm or more in Breslow thickness, we demonstrated a negative association between narrow margins and loco-regional relapse free survival (defined as local recurrence, in-transit metastases and regional lymph node metastases) (multivariable adjusted hazard ratio 1·34; 95% CI 1·06-1·71, P=0·02).[10] There were no statistically significant differences between the two groups in either melanoma-specific survival or overall survival. We now report extended follow-up of this trial with a median follow-up of 106 months.

Methods

Study Design and participants

The study design, patient eligibility criteria, trial protocol, and endpoints have been previously described in detail.[10] Briefly, 900 patients with a single primary localised cutaneous melanoma greater than 2mm in Breslow thickness arising on the trunk or limbs (not including soles of feet or palms of hands) were randomised using 1:1 ratio to either a 1cm surgical excision or a 3cm surgical excision as the measured clinical margin taken around the primary melanoma lesion. Patients were recruited from centres in the UK and Poland and the trial was performed under the auspices of the UK Melanoma Study Group, the British Association of Plastic Surgeons, and the Scottish Cancer Therapy Network. It was approved by the local ethics committees of all participating centres. Written informed consent was obtained for all participants.

Randomisation and masking

Randomisation by random permuted blocks was performed centrally at The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) and was stratified according to centre and extent of primary surgery (1mm initial margin of excision or 1cm initial margin of excision).

Procedure

The primary tumour could be excised before randomisation, with either a 1mm or 1cm margin to confirm the diagnosis and determine the thickness of the lesion (Figure 1). If further surgery was required by the patient's allocation, it was to be performed within 45 days of primary excision. The method of surgical closure was at the discretion of the participating surgeon. Elective lymph node dissection and sentinel node biopsy were not part of routine practice at the time the trial was conducted. Adjuvant chemotherapy was not permitted in the trial protocol. Recruitment began in 1993 and closed in 2001. To maximise survival data ascertained, UK patients (n=790)

were traced for their vital status and in January 2012 the death certificates of patients known to have died were requested in order to identify the cause of death as stated on the death certificate. Death certificates were not obtained for non-UK patients (n=110); follow-up in these patients is largely limited to 5 years. Death was classed as melanoma-specific if the cause of death was reported as melanoma on the clinical trial death case report form or if there was any evidence of distant metastatic melanoma at the time of death (as reported in patient files or on death certificates). Attribution of the cause of death as stated on the death certificate to either melanoma specific or non- melanoma death was blinded to treatment group.

Outcomes

The primary endpoints of the trial were loco-regional recurrence and disease-free survival; due to limited ability to collect recurrence data in later years these endpoints are not reassessed in the present long term analysis. The secondary endpoints were overall survival, measured as time from randomisation to death from any cause, and melanoma-specific survival, measured as time from randomisation to death reported to be from melanoma.

Statistical Analysis

All analyses were by intention to treat. For the overall survival endpoint, patients not known to have died were censored at the date of last follow-up. For the melanoma-specific survival endpoint, patients who died of non-melanoma causes were censored at the time of death and patients who died from an unknown cause were censored on the day prior to their date of death. Patients who are not known to have died were censored at the date of their last visit. To assess the robustness of these assumptions we conducted a competing risks analysis treating confirmed non-melanoma deaths as the competing event.

Kaplan-Meier curves[11] were constructed and treatment groups were compared using the log-rank test. The effect of individual prognostic factors was assessed in a multivariable analysis

using the same Cox proportional hazard model[12] as in our previous report,[10] adjusting for age; hazard ratios (with 95% confidence intervals) are presented, with hazard ratios greater than 1 indicating a disadvantage to the 1cm margin group relative to the 3cm margin group. The proportionality assumption of the Cox model was tested with Schoenfeld residuals and not found to be violated. For the competing risks analysis, cumulative incidence functions for each cause of death (melanoma and non-melanoma) were plotted and treatment groups compared by means of Gray's test. Hazard ratios were obtained from the univariate Fine & Gray model.[13,14] A multivariable analysis was also performed using Fine and Gray's model, including the same variables as the multivariable Cox model.

A subgroup analysis was conducted to assess whether there was a difference in the effect of margin width with sex, tumour thickness, age group, site, ulceration, and according to surgical policy as protocol defined (proposed vs. alternative, see Figure 1). Wald tests were used to compare the hazard ratios between subgroups. To make some compensation for multiplicity, for subgroup analysis P-values of less than 0·01 were deemed significant. Two sided significance tests were used throughout.

The snapshot used for the current analysis was taken on 31/08/2012 after information from the death certificate analysis had been obtained. This was the first and only analysis that had been performed on this data set since the initial report of this trial. Analyses were performed using STATA version 11.2, except competing risks analysis, which was conducted in R 3.0.2.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. One of the senior authors (JMT) is a trustee of the Meirion Thomas Cancer Research fund that funded the administrative fee required to retrieve copies of death certificates for patients within the trial. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 1993 and 2001, 453 patients were randomised to a 1cm surgical margin and 447 patients to a 3cm margin (Figure 1). Baseline characteristics were well balanced between the two groups, with an overall median age at entry of 58·7 years (IQR 47·2-69·2). Median tumour thickness was 3·0mm in the 1cm group and 3·1mm in the 3cm group and ulceration was present in 33·1% of patients (31·8% in the 1cm group and 34·5% in the 3cm group). Full details of the trial procedures and baseline characteristics were reported in the original publication.[10] Overall median follow-up is 68 months (5·7 years; IQR 2·9-8·6 years) and median follow-up in patients not known to have died (censoring at death) is 8·8 years; (106 months IQR 76-135 months). Median follow-up for the UK patients in whom a death certificate analysis was performed (censoring at death) is 111 months (IQR 82-141 months). To date, a total of 494 deaths have been reported; 359 of these were death from melanoma. For three participants melanoma was present at the time of death but this was not the cause of death and a total of 125 participants died from other causes. Cause of death is unknown for ten patients. Four patients did not have any follow-up after randomisation and are censored at 1 day.

Figure 2 shows Kaplan-Meier survival curves for overall survival (Panel A) and melanoma-specific survival (Panel B). There were 253 deaths overall in the 1cm margin group and 241 in the 3cm group (unadjusted hazard ratio 1·14; 95% CI 0·96 to 1·36; P=0·143). There were 194 deaths from melanoma in the 1cm margin group, compared with 165 in the 3cm margin group. Univariable analysis (i.e. unadjusted) showed that the risk of death from melanoma was 24% higher in the 1cm margin group compared with the 3cm margin group (hazard ratio 1·24; 95% CI 1·01 to 1·53; P=0·041). The estimated absolute difference in melanoma-specific survival at 10 years between the two groups was 5.95% (95% CI -0.54%, 12.44%).

A total of 773 patients had complete data on all the factors included in the multivariable analysis. The effect of a 1cm margin compared with a 3cm margin was similar by multivariable

analysis adjusting for known prognostic factors (hazard ratio for overall survival 1·19; 95% CI 0·99 to 1·45; P=0·070; hazard ratio for melanoma-specific survival 1·28; 95% CI 1·02 to 1·61; P=0·031) (Table 1). Interactions between margin width and sex, tumour thickness, age group, site and ulceration were tested in a post hoc analysis for statistical significance with respect to overall survival and melanoma-specific survival (Figure 3, Panels A and B). None of the interactions reached a P value of less than 0·01, showing no strong evidence that a poorer prognosis associated with a 1cm margin of excision was specific to a particular subgroup of patients.

The results for melanoma-specific deaths were robust with a competing risks analysis for death. Figure 4 shows the estimated cumulative incidence curves according to cause of death. The cumulative incidence of death from melanoma taking into account competing deaths due to other causes was 24% higher in the 1cm margin group compared to the 3cm margin group (hazard ratio 1·24; 95% CI 1·01 – 1·52; Gray's test P-value 0·036). The multivariable analysis performed with Fine and Gray's model for melanoma-specific deaths showed similar results to the Cox model for melanoma-specific survival shown in Table 1 (results not shown). No differences between the two margins were observed regarding the cumulative incidence of deaths due to other causes. Only age was a prognostic factor for non-melanoma deaths (HR 4·06; 95% CI 2·62 – 6·32, p<0·001). When the rates of death from melanoma and from other causes estimated by the competing risks analysis were calculated for different age groups, the non-melanoma death rate was negligible for younger age groups but became the predominant cause of death in later years of follow-up for older patients (Table 2).

Discussion

We report the long term survival results of a randomised comparison of 1cm versus 3cm excision margins in high risk primary melanoma (2mm or more in thickness). The principal finding is that at a median follow-up of 106 months there was a statistically significant difference in melanoma-specific survival with a 24% increase in the risk of death from melanoma in the narrow margins group (p=0.047)_ . There was an estimated 14% increase in risk of death from any cause in the 1cm excision group compared with the 3cm group although this result was not statistically significant.

As death certificates were collected for UK patients only, a sensitivity analysis was performed including only UK patients and, with hazard ratios of 1.11 (95% CI 0.92, 1.33) and 1.21 (95% CI 0.97, 1.50) for overall survival and melanoma-specific survival respectively, the results were consistent with the primary result. Our previous report[10] with a median follow-up of 5 years showed that a 1cm excision margin was associated with a significant increase in loco-regional relapse when compared with a 3cm excision margin in patients with high risk melanoma. In that report, although there was a difference in the number of deaths in the two study groups, it was not statistically significant (128 deaths from melanoma in the group with 1cm excision margins, as compared with 105 in the group with 3cm excision margins (hazard ratio 1·24; 95% CI 0·96 to 1·61; P=0·1)). There was no observed difference in overall survival between the two groups (32·2% in the 1cm group compared with 30·9% in the 3cm group - hazard ratio, 1·07; 95% CI 0·85 to 1·36; P=0·6).

The current analysis does not include an updated analysis of the loco-regional recurrence endpoint as follow-up data for loco-regional relapse beyond five years are sparse. This report describes analyses only of melanoma-specific and overall survival and demonstrates a statistically significant effect on melanoma-specific survival (HR 1·24; 95% CI 1·01 to 1·53; P=0·041). Loco-regional relapse is the most common first site of relapse of metastatic

melanoma and accordingly an increased risk of loco-regional relapse in the narrow margin group may indicate an increased future risk of melanoma-specific death. During the period of this study, when there were no effective systemic therapies for metastatic melanoma, stage 4 disease was associated with a very poor prognosis with a median survival of between 8 and 18 months depending on the pattern of metastatic spread.[15]

In this study there was no significant difference in the overall survival rate between the 1cm and 3cm groups despite a significant difference in melanoma-specific survival. While age, gender, tumour thickness, ulceration, and tumour site all appear to be prognostic factors for overall survival, only age was found to impact non-melanoma deaths, with the non-melanoma death rate being similar between the 1cm and the 3cm groups.

As sentinel node biopsy was not performed routinely in this trial,[10] there exists the possibility that the trial groups were imbalanced in terms of clinically occult disease within regional lymph nodes at the time of randomisation which could have biased the outcome of the trial. However, treatment allocation was by randomisation which aims to ensure there are no systematic differences between the two groups in either known or unknown prognostic factors. Any imbalances in unobserved factors in this study are due to chance and a chance imbalance in a study of this size is unlikely to impact outcome. As the trial groups were well balanced in terms of other known prognostic factors for outcome at the time of trial recruitment (sex, tumour thickness, disease site) and ulceration was slightly more prevalent in the 3cm group (39·8% ulceration rate in the 3cm group vs 36·6% in the 1cm group), it would seem unlikely that the sentinel node status would be worse in the 1cm group than in the 3cm group, although a chance imbalance remains possible.

This study cannot determine if loco-regional relapse is causally related to the subsequent development of distant metastatic disease, or whether the development of loco-regional disease is merely correlated with and predates the development of metastatic disease. However, a 1cm clinical margin should be adequate to completely excise a primary melanoma with negative

microscopic margins. As a 3cm margin resulted in a decreased rate of melanoma deaths, this would suggest that surgically intervening in a micro-metastatic process in the 3cms around the primary tumour can somehow impact on the later metastatic process at more distant sites. Previous studies have shown a statistically significant increase in local recurrence rates after 1cm excisions,[6,16] suggesting 1cm margins may not be adequate to deal with local micro satellitosis.

Previous randomised studies of elective[17-21] or selective[22] lymph node dissection have not shown a statistically significant in difference melanoma-specific survival from the point of randomisation. The lack of a proven survival benefit in these nodal studies is at odds with the likely biological hypothesis for an effect on survival shown in this study i.e. that removal of microsatellites around the primary tumour influences the development of metastatic disease. However as subgroup analyses in these studies raised the possibility of survival benefit for prophylactic lymph node clearance that was not demonstrable at the point of randomisation[22] it is possible that there is a consistent biological process underlying the effect seen in this study and in previous studies of prophylactic lymph node clearance.

Current international guidelines advise a 2cm excision for melanomas greater than 2mm in thickness and the other major randomised study for thick melanomas[6] showed conclusively that a 4cm excision was not superior to a 2cm excision in terms of melanoma-specific survival. Hence while our study has suggested that a 1cm margin appears inadequate for excision of melanomas thicker than 2mm, it does not necessarily follow that margins greater than 2cm need to be undertaken. This study has re-emphasised that the choice of surgical margins taken around a cutaneous melanoma is important and for the first time provides evidence to suggest that a narrower excision margin used for thick primary tumours influences melanoma-specific survival. This may be pertinent for certain melanomas for which narrow (1cm) margins are presently advised, such as melanomas between 1mm and 2mm in thickness but with other adverse prognostic features (ulceration and/or high mitotic rate). The possible difference

between a 1cm and 2cm margin in melanomas greater than 1mm in thickness is currently under investigation in an on-going randomised trial.[23]

Acknowledgements

The authors acknowledge the contributions of all patients who kindly agreed to join the trial and the efforts of all of the contributors and institutions as cited in the initial report of this trial.[10] The authors thank Roger A'Hern for his statistical input.

Author contributions

Andrew John Hayes is the corresponding author and was responsible for reviewing data, guiding analyses, and interpreting results. Lauren Maynard was responsible for planning and conducting statistical analyses. Gillian Coombes was responsible for trial coordination and collection of clinical data. Julia Newton-Bishop, Michael Timmons, Martin Cook, and Jeffery Theaker were responsible for recruitment of patients and collection of clinical data. Judith Bliss was responsible for guiding and planning statistical analyses and interpretation of results. Joseph Meirion Thomas was the chairman of the trial administration working party and was also responsible for recruiting patients and collection of clinical data. Judith Bliss and Joseph Meirion Thomas contributed equally to the research and are joint senior authors.

All authors were involved in the writing, review, and approval of the final manuscript. All authors agreed to the submission of the final version of the manuscript.

Conflicts of interest

The authors have no conflict of interest to declare.

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Research in context

Evidence before this study

Five randomised trials[3–7] have analysed the effect of surgical margins on outcomes in cutaneous melanoma. No previous trial has shown a significant effect on the choice of surgical margins on either loco-regional relapse or melanoma-specific survival. However, some of these studies have shown non-significant tendencies favouring wider margins in minimising loco-regional and distant relapse.

Added value of this study

This study reports on long term survival analysis and is the first to show that wider surgical margins also result in a statistically significant improvement in melanoma-specific survival.

Implications of all the available evidence

This study, alongside the other randomised trials, reiterates current international guidelines stating that a 1cm margin is inadequate for the treatment of a melanoma greater than 2mm in Breslow thickness. It would lend support to further investigation of the adequacy of a 1cm margin for melanomas between 1mm and 2mm in thickness, especially those with other poor prognostic features, for which most international guidelines at present still advise a 1 cm excision.

Figure Legends

Figure 1 Trial Profile.

Figure 2 Kaplan-Meier plot for Overall Survival (Panel A) and Melanoma-Specific Survival (Panel B). Hazard Ratios and confidence intervals are at a median follow-up of 106 months.

Figure 3 Subgroup analyses showing interactions between margin width and sex, tumour thickness, age group, site and ulceration with respect to Overall Survival (Panel A) and Melanoma-Specific Survival (Panel B). The red line shows the hazard ratio in all patients. No statistically significant differences between subgroups; there was no evidence that a poorer prognosis associated with 1cm excision margin was specific to a particular subgroup of patients. *99% CIs presented for subgroups; 95% CI presented for all patients

Figure 4

Cumulative incidence functions for Death due to Melanoma (Panel A) and Death due to Other Causes (Panel B). Hazard ratios are obtained from the (unadjusted) Fine and Gray's model and P-values from the Gray test to compare cumulative incidence functions.

Table 1

Multivariable analysis of Overall Survival and Melanoma-Specific Survival.

				Overall survival			Melanoma-specific survival		
		N	%	HR	95% CI	P value#	HR	95% CI	P value#
Margin	3cm	388	50.2%	1.00			1.00		
	1cm	385	49.8%	1.19	0.99 1.45	0.07	1.28	1.02 1.61	0.031
Sex	Female	354	45.8%	1.00			1.00		
	Male	419	54.2%	1.38	1.11 1.71	0.003	1.38	1.07 1.77	0.013
Tumour thickness* (mm)		773	100.0%	1.18	1.1 1.27	<0.001	1.23	1.13 1.33	<0.001
Ulceration	Absent	477	61.7%	1.00			1.00		
	Present	296	38.3%	1.68	1.38 2.04	<0.001	1.74	1.39 2.19	<0.001
Site	Distal limb	244	31.6%	1.00			1.00		
	Proximal limb	174	22.5%	1.23	0.93 1.63	0.029	1.46	1.04 2.05	0.003
	Trunk	355	45.9%	1.41	1.09 1.81		1.71	1.26 2.31	
Age (years)	<60	479	53.2%	1.00			1.00		
	≥60	421	46.8%	1.49	1.23 1.81	<0.001	1.12	0.89 1.39	0.339

P value from Wald test

*Tumour thickness categorised as 0-2.49mm, 2.5-3.49mm, 3.5-4.49mm, 4.5-5.49mm, ≥5.5mm and fitted as linear trend

Table 2

Death rates from melanoma and other causes in different age groups at 2-year intervals from randomisation

	Age of patient at randomisation				
	<45 years N=180	45 - 53 years N=185	54 - 63 years N=190	64 - 70 years N=161	71+ years N=184
N alive at 2 years	**159**	**157**	**155**	**143**	**138**
Total N deaths ≤2y	**18**	**27**	**30**	**15**	**46**
*Deaths from:					
melanoma	17 (10·6%)	27 (17·1%)	27 (17·2%)	14 (9·7%)	36 (26·1%)
other cause	1 (0·6%)	0 (0·0%)	3 (1·9%)	1 (0·7%)	10 (7·3%)
N alive at 4 years	**121**	**129**	**127**	**112**	**105**
Total N deaths 2.01-4y	**29**	**22**	**17**	**24**	**32**
*Deaths from:					
melanoma	29 (23·1%)	21 (15·9%)	17 (12·9%)	22 (19·1%)	21 (20·0%)
other cause	0 (0·0%)	1 (0·8%)	0 (0·0%)	2 (1·8%)	11 (10·5%)
N alive at 6 years	**80**	**90**	**93**	**76**	**81**
Total N deaths 4.01-6y	**13**	**13**	**16**	**21**	**20**
*Deaths from:					
melanoma	13 (13·7%)	12 (11·2%)	13 (12· 6%)	16 (19·6%)	12 (14·5%)
other cause	0 (0·00%)	1 (1·00%)	3 (3·0%)	5 (6·3%)	8 (9·6%)
N alive at 8 years	**49**	**60**	**56**	**47**	**54**
Total N deaths 6.01-8y	**5**	**4**	**12**	**14**	**16**
*Deaths from:					
melanoma	4 (6·7%)	2 (2·6%)	7 (10·8%)	10 (18·5%)	6 (9·9%)
other cause	1 (1·8%)	2 (3·1%)	5 (7·2%)	4 (7·0%)	10 (17·0%)
N alive at 10 years	**30**	**29**	**30**	**26**	**23**
Total N deaths 8.01-10y	**5**	**5**	**1**	**5**	**21**
*Deaths from:					
melanoma	5 (13·80%)	3 (6·8%)	0 (0·0%)	1 (2·5%)	7 (23·9%)
other cause	0 (0·0%)	2 (3·9%)	1 (3·2%)	4 (11·6%)	14 (49·9%)
N alive at 12 years	**8**	**11**	**15**	**9**	**13**
Total N deaths 10.01-12y	**2**	**1**	**4**	**5**	**6**
*Deaths from:					
melanoma	2 (13·1%)	1 (4·8%)	1 (4·3%)	1 (6·1%)	1 (6·3%)
other cause	0 (0·0%)	0 (0·0%)	3 (15·5%)	4 (34·0%)	5 (31·8%)

*Deaths presented as N (rate), where rate is approximated, for each cell, as the probability of dying from each specific cause in the 2-year interval, given the patient is alive at the beginning of the 2-year interval using cumulative incidence functions from the competing risks analysis

Note: cut points for age were selected using quintiles rounded to the nearest whole number

Web appendix

Baseline characteristics

	1cm margin N=453		3cm margin N=447		Total N=900	
	N	%	N	%	N	%
Gender						
Male	248	54·75%	220	49·22%	468	52·00%
Female	205	45·25%	227	50·78%	432	48·00%
Age						
<60 years	243	53·64%	236	52·80%	479	53·22%
≥60 years	210	46·36%	211	47·20%	421	46·78%
Median (IQR)	58·7	(47·1, 68·8)	58·7	(47·3, 70·1)	58·7	(47·2, 69·2)
Tumour thickness (mm)						
<2·5	133	29·36%	114	25·50%	247	27·44%
2·5-3·49	136	30·02%	144	32·21%	280	31·11%
3·5-4·49	77	17·00%	77	17·23%	154	17·11%
4·5-5·49	40	8·83%	40	8·95%	80	8·89%
≥5·5	65	14·35%	72	16·11%	137	15·22%
Missing	2	0·44%	0	0·00%	2	0·22%
Median (IQR)	3	(2·3, 4·2)	3·1	(2·4, 4·5)	3	(2·4, 4·2)
Tumour thickness (mm) UICC* categorisations						
≤1	0	0·00%	2	0·45%	2	0·22%
1·01-2·00	55	12·14%	44	9·84%	99	11·00%
2·01-4·00	280	61·81%	275	61·52%	555	61·67%
>4	116	25·61%	126	28·19%	242	26·89%
Missing	2	0·44%	0	0·00%	2	0·22%
Site						
Distal	136	30·02%	140	31·32%	276	30·67%
Proximal	108	23·84%	97	21·70%	205	22·78%
Trunk	203	44·81%	206	46·09%	409	45·44%
Missing	6	1·32%	4	0·89%	10	1·11%
Ulceration (>1mm)						
Absent	249	54·97%	233	52·13%	482	53·56%
Present	144	31·79%	154	34·45%	298	33·11%
Not assessed	60	13·25%	60	13·42%	120	13·33%
Initial surgery						
Proposed (1mm)	372	82·12%	370	82·77%	742	82·44%
Alternative (1cm)	81	17·88%	77	17·23%	158	17·56%

*UICC: Union for International Cancer Control