

1 **A retrospective study of one versus two cm excision margins for cutaneous malignant**
2 **melanomas thicker than two mm**

3 **Type of study** Original Article

4 Robert E. Hunger, M.D., Ph.D.¹, Sarina Angermeier², S. Morteza Seyed Jafari, M.D.^{2,3},
5 Adrian Ochsenbein, M.D.⁴, Maziar Shafighi, M.D.^{2*}

6 1 University clinic for Dermatology, Bern University Hospital, Inselspital, Bern,
7 Switzerland

8 2 University clinic for Plastic, Reconstructive and Hand Surgery, Bern University
9 Hospital, Inselspital, University of Bern, Bern, Switzerland

10 3 Graduate School for Cellular and Biomedical Sciences, University of Bern,
11 Switzerland.

12 4 University clinic for Medical Oncology, Bern University Hospital, Inselspital,
13 University of Bern, Bern, Switzerland

14

15 ***Corresponding author**

16 Maziar Shafighi

17 University clinic for Plastic, Reconstructive and Hand Surgery, Bern University Hospital,
18 Inselspital, University of Bern, Bern, Switzerland

19 Tel: +41 31 632 8014

20 E-Mail: maziar.shafighi@insel.ch

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22 **Running head** one versus two cm excision margins for melanomas thicker than 2
23 mm

24

25 **ABSTRACT**

26 **Background:** Most guidelines recommend at least two cm excision margin for melanomas
27 thicker than two mm.

28 **Objective:** We evaluated whether one or two cm excision margins for melanoma (> 2 mm)
29 result in different outcomes.

30 **Methods:** This is a retrospective cohort study on patients with melanomas (> 2 mm) who
31 underwent tumor excision with one cm (228 patients) or two cm (97 patients) margins to
32 investigate presence of local recurrences, locoregional and distant metastases, disease-free
33 and overall survival.

34 **Results:** Three hundred twenty-five patients with mean age of 61.84 years and Breslow
35 thickness of 4.36 mm, were considered for the study with a median follow-up of 1852 days
36 (1995- 2012). There was no significant difference in the frequency of locoregional and
37 distant metastasis between the two groups ($P = 0.311, 0.571$). The survival analysis
38 showed no differences for disease-free ($P = 0.800$; HR, 0.948; 95% CI 0.627 to 1.433) and
39 overall-survival ($P = 0.951$; HR, 1.018; 95% CI 0.575 to 1.803).

40 **Limitations:** The study was not prospectively randomized.

41 **Conclusions:** Our study did not show any significant differences in important outcome
42 parameters like local- or distant metastases, overall survival. A prospective study testing
43 one versus two cm excision margin is warranted.

44 **Key words** Disease free survival; Margin of excision; Melanomas thicker than 2 mm;
45 Metastases; Overall survival; Recurrences

46 INTRODUCTION

47 One of the major controversies in the primary management of melanoma is how much
48 surrounding normal skin should be excised around a primary cutaneous melanoma.¹⁻⁴

49 Balancing cosmesis, function and morbidity with oncologic outcomes requires careful
50 decision-making with respect to determination of the appropriate margins.⁵ Inadequate
51 excision margins increase the risk of local recurrence.⁶ Conversely, unnecessarily large
52 margins of excision generate greater morbidity and increased costs.⁴ Overall survival,
53 disease-free survival, and local recurrence rates are not improved by excision margins
54 greater two cm.⁷ Therefore, a two cm excision margin is recommended for melanomas
55 thicker than two mm in most clinical guidelines.^{4,7}

56 In our clinics a 1cm excision margin is the approved standard by the regional Melanoma
57 Board for melanoma thicker than two mm, whereas external consultants operated with a
58 two cm excision margin. We now analyzed in a retrospective study over a period of 16-
59 years whether 1 cm surgical excision margin has caused any disadvantages in important
60 outcome parameters, in comparison to two cm margins.

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63 **METHODS**

64 **Study Population**

65 We performed a population-based survey of melanoma management (registered in
66 ClinicalTrials.gov, trial number NCT02088762) using a database of patients from the Bern
67 University Hospital. The study period ranged from May 1995 to May 2012, with follow-up
68 until the end of July 2013. All cases of single, primary, localized, cutaneous melanoma
69 tumors with > two mm thickness without evidence of metastasis at the time of surgery and
70 treated by excision of the lesion were included in the study. Patients without documented
71 surgical margins or follow-up were excluded. This study was conducted in accordance
72 with the standards of the Ethical Committee of the Canton of Bern (KEK number: 24-08-
73 10) on human experimentation and with the Helsinki Declaration of 1975, as revised in
74 1983.

75

76 **Procedures**

77 We collected data on patient gender, age, tumor location, tumor type, Breslow thickness,
78 and presence of ulceration, distant and locoregional metastases. All surgeons were board
79 certified and accredited members of an established cancer cooperative group.
80 During the 17-year time period, two consultants performed primary melanoma excision
81 according to the current accepted guidelines, using a 2 cm margin (two cm group). All
82 other consultants excised all melanoma in accordance with our regional Melanoma Board
83 approved guideline with a one cm margin irrespective of Breslow thickness (one cm
84 group). Thus, the excision margins were dependent on the referral to the individual
85 consultant. In all cases, sentinel lymph node biopsies were taken. An experienced
86 pathologist from the University Hospital Bern reviewed the excised tissues and the slides
87 were also evaluated by a panel of melanoma pathologists, who independently reviewed a
88 representative histologic section of each.

89 In the current study, local recurrences can represent either persistent disease due to
90 inadequate initial excision or true recurrence adjacent to the scar after adequate prior wide
91 local excision and usually have an in situ component, or they may represent satellite
92 metastases. Locoregional recurrence of melanoma after initial resection was defined as
93 recurrence at the site of the primary lesion, regionally in the draining lymph node basin, or
94 anywhere in between (local recurrence cases were not included).⁸⁻¹⁰ Spreading from the
95 original (primary) tumor to distant organs or distant lymph nodes was considered as distant
96 metastases.¹¹

97 Local recurrence rates, locoregional and distant metastases, death attributed to melanoma,
98 disease-free survival, and overall survival were compared between the two groups.

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100 **Statistical Analysis**

101 All analyses were conducted using the Statistics Package for the Social Sciences (spss;
102 SPSS Inc., Chicago, IL, USA) version 21.0. All p values relate to two-sided tests with an
103 alpha level of 0.05. For categorical patient characteristics, Fisher's exact test was used to
104 detect differences between groups. Disease-free survival was estimated using the Kaplan-
105 Meier method. The confidence intervals of hazard ratios for Cox regression and overall
106 survival (for time-to-event variables) were calculated. P value was based on the Log Rank
107 (Mantel-Cox) test to check whether the two groups had different overall survival functions.
108 *P* value < 0.05 was considered significant.

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111 RESULTS

112 Of all patients with malignant melanoma treated in our center between May 1995 and May
113 2012, 325 (138 female, 187 male) patients with melanoma thicker than 2 mm with a
114 median age of 61.84 ± 14.71 years (mean \pm SD) fulfilled the inclusion criteria (Fig 1). The
115 median follow-up for the patients was 1852 days. The mean \pm SD Breslow's depth of the
116 study patients' primary melanoma tumors was 4.36 ± 3.99 mm (2.10 – 45.00 mm). Two
117 hundred twenty lesions (67.7 %) revealed an infiltration thickness \leq four mm, while 105
118 (32.3 %) were thicker than four mm. Nodular melanoma was the most frequent (68.3 %) and
119 amelanotic melanoma the least frequent (1.8 %) type in our study population.
120 Furthermore, the trunk area was the most frequent primary tumor location (39.4%). One
121 hundred forty patients (43.1 %) had ulceration in their tumors, 106 patients (32.6 %) presented
122 with positive sentinel lymph node biopsies, and death was attributable to melanoma in 54 patients
123 (16.6%).
124 Two hundred twenty eight patients underwent tumor excision with a one cm skin margin
125 while the tumors of the other 97 patients were excised with a two cm margin.
126 Statistical analysis of tumor characteristics (tumor thickness, primary tumor location, tumor
127 type, and sentinel lymph node metastasis) did not reveal significant differences
128 between the two groups, except for ulceration, which was detected significantly more often
129 in the one cm group (Table 1).
130 Local recurrence occurred in 11 patients (3.4 %), locoregional metastases in 74 patients
131 (22.8 %) and distant metastases in 77 (23.7 %). Although ulceration was seen more
132 frequently in the one cm group, this did not result in a significant difference in local
133 recurrence ($P = 0.739$), locoregional ($P = 0.311$) and distant metastases ($P = 0.571$) during
134 the follow-up period. Death attributable to melanoma was also not significantly different
135 between our study groups (18.8 % vs. 18.6 %, respectively) (Table 2).

136 Kaplan-Meier methods comparing disease-free and overall survival did not reveal a
137 significant difference between the one cm group and the two cm group ($P = 0.800$ and
138 0.951 , respectively). In Cox regression analysis of the patients with one cm excision
139 margins vs. the patients with two cm excision margins, the estimated hazard ratios for
140 disease-free survival and overall survival were 0.948 (95% confidence interval, 0.627 to
141 1.433) and 1.018 (95% confidence interval, 0.575 to 1.803), respectively (Tables 3, Fig 2-
142 3).

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145 **DISCUSSION**

146 Guidelines for melanoma treatment emphasize the importance of complete surgical
147 excision.¹²⁻¹⁵ However, selection of an adequate excision margin is one of the major
148 controversies in the management of primary cutaneous melanomas, especially in
149 melanoma thicker than two mm.^{1, 3, 4} In light of the tendency to narrow the excision
150 margins in primary melanoma thicker than two mm treatment, Gillgren, P et al. performed
151 a randomized controlled trial in this patient group that compared a two cm versus a four cm
152 surgical resection margin. Their findings suggested that a two cm resection margin is
153 sufficient and safe for patients with cutaneous melanoma thicker than two mm.³ As a
154 result, currently, most protocols suggest at least a two cm excision margin for melanoma >
155 two mm in depth.¹⁶⁻¹⁸

156 In order to follow this way to have a narrower but safe excision margins in primary
157 melanoma treatment, we retrospectively analyzed the outcome of patients with melanomas
158 thicker than two mm (2.10 – 45.00 mm in thickness) using a one or a two cm excision
159 margin. Although our study was not prospectively randomized, the two study population
160 were balanced for important prognostic factors with the exception of ulceration, which was
161 more frequent in the group with narrower excision margin (Table 1). In this study, we did
162 not detect a statistically significant increase in locoregional metastases, distant metastases
163 or a decrease in disease-free or overall survival in patients undergoing a resection with
164 only 1 cm margin.

165 We observed more locoregional and distant metastases in the patients with two cm
166 excision margins, but these differences were not statistically significant. Similarly,
167 Gillgren et al. reported less distant metastasis in the group with narrower excision margins
168 (two cm) versus the wider excision (four cm). This difference might raise the idea that
169 selection of wider excision margins may increase the risk of locoregional and distant
170 metastases.

171 Gillgren et al. reported that 14.53% of patients died by melanoma,³ while death attributable
172 to melanoma was seen in 16.6 % of our patients, which was not significantly different
173 between the groups in our study ($P = 0.625$). Thomas et al. reported deaths in 28.26% of
174 the group with 1 cm margins and 23.49 % of the group with 3 cm margins.⁴ Moreover,
175 Thomas et al. found a significant increase in the risk of death from melanoma associated
176 with a narrow margin of excision in comparison to a wide margin after evaluation of their
177 results and Swedish Melanoma Study Group trial ($P = 0.008$).^{4, 19}
178 Furthermore, Kaplan-Meier methods and Cox regression analysis of our groups showed no
179 evidence of significant differences in disease-free survival and overall survival. Likewise,
180 in Thomas et al.'s study on high-risk melanoma, a similar overall survival rate ($P = 0.6$;
181 HR, 1.07; 95% confidence interval 0.85 to 1.36) was reported between the groups with 1
182 cm and 3 cm excision margins. Nevertheless, due to the increased risk of melanoma related
183 death in the group with narrow excision margins, the authors concluded that the use of a
184 one cm margin should be avoided in patients with melanomas ≥ 2 mm thickness.⁴
185 In summary, despite various studies, clear evidence that increasing excision margins
186 improves overall-survival is currently missing.¹⁶ Furthermore, decision about the need for
187 two cm margins for thicker melanomas is still an important controversy. As a result there is
188 a demand for further studies to overcome these issues. We believe that modification of
189 current approved guidelines which are based on important clinical studies should be only
190 performed carefully after implementation of prospective randomised multicenteric clinical
191 trials. However, despite several limitations (being retrospective, and non-randomized, and
192 having relative short follow-up), the result of the current study suggests that excision of
193 melanomas thicker than two mm with one cm excision margin is safe and results in a
194 similar outcome as a two cm excision margin. Therefore, this study highlights the possible
195 hope for future, and may provoke the important melanoma centers to set up new
196 randomized controlled trials with longer follow-up to revise current melanoma guidelines.

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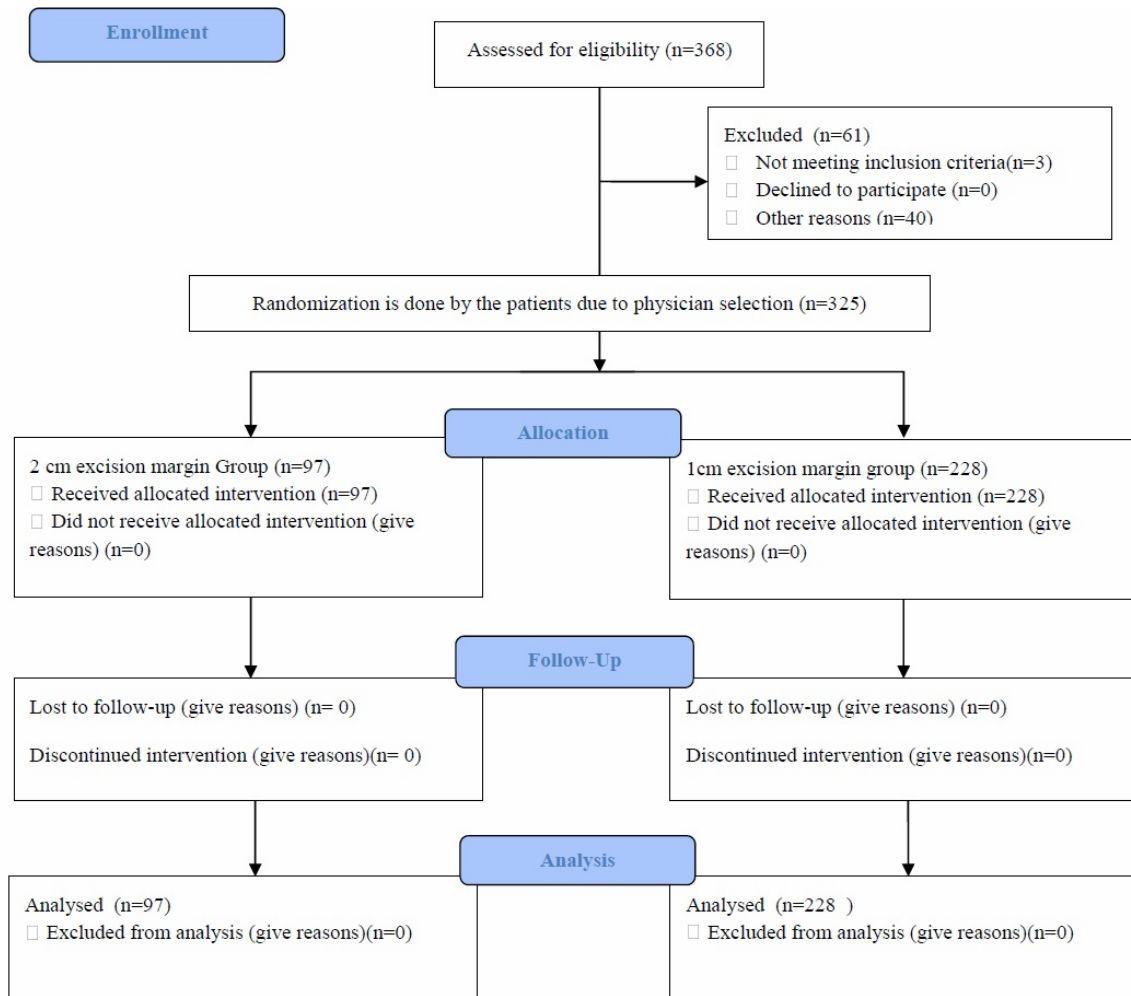
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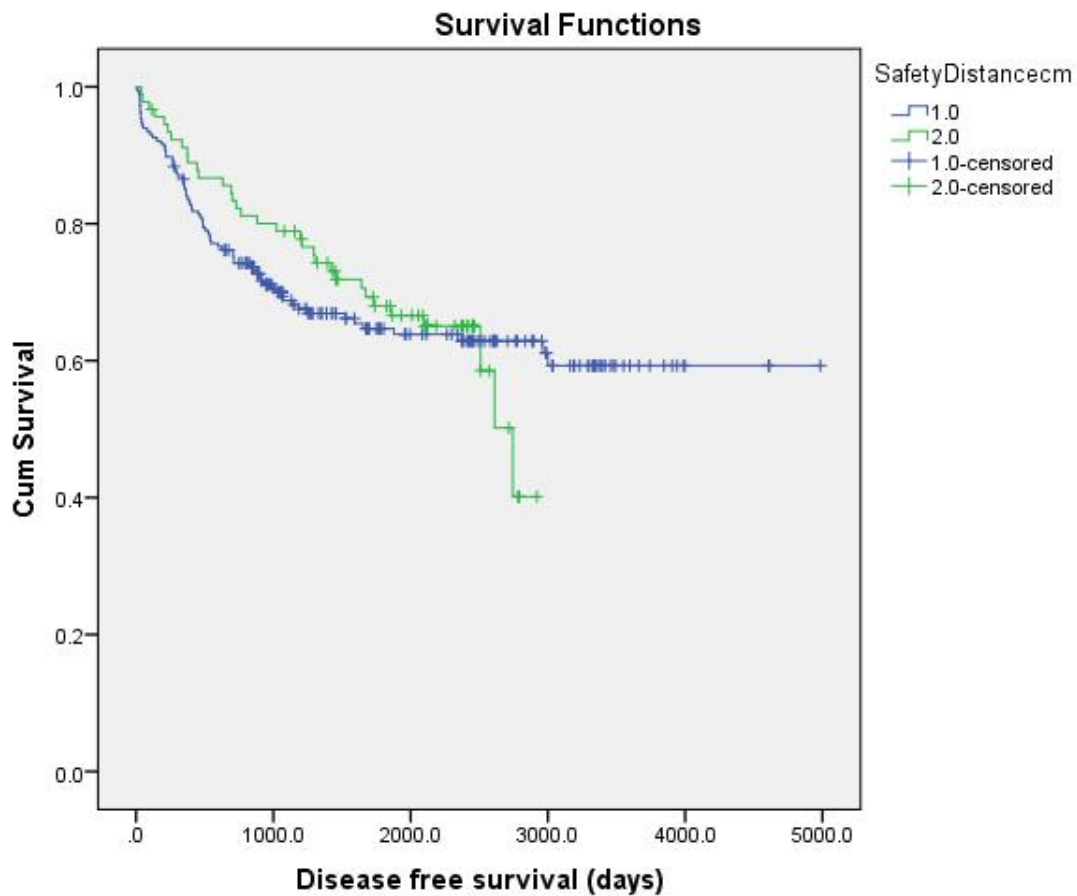
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254 **Figure:**



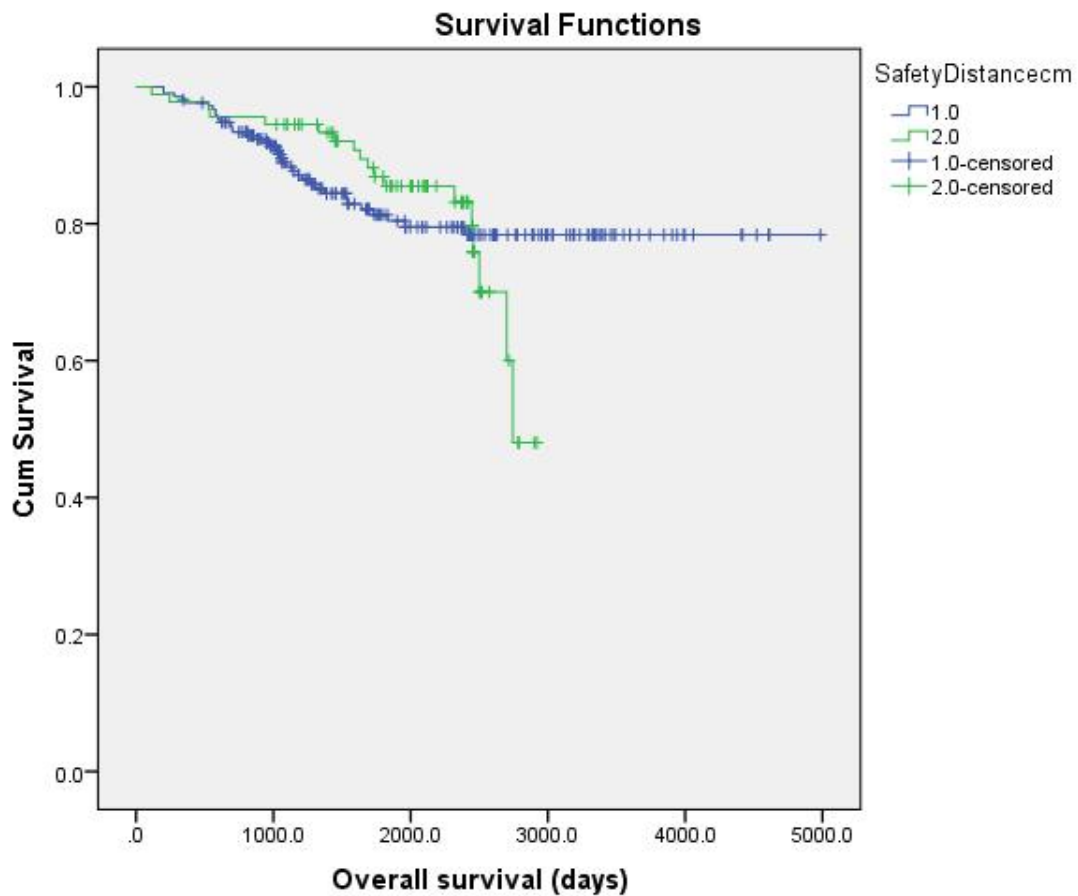
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256 **Fig. 1. Patient disposition**



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258 Fig. 2. Disease-free survival according to primary melanoma site (log-rank test, $P = 0.800$).



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260 Fig. 3. Overall survival (log-rank test, $P = 0.951$)

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262 Tables:

263 TABLE 1. Study patients' characteristics

Characteristics		Margin of surgery		<i>P</i>
		1 cm	2 cm	
Mean follow-up in years		5.18	5.51	0.207
Tumour thickness [Breslow] (Mean ± SD mm)		4.22 ± 2.81	4.67 ± 5.90	0.479
Sex	No. of Female patients (percent)	98 (42.98%)	40 (41.24%)	0.807
	No. of Male Patients (percent)	130 (57.02%)	57 (58.76%)	
Primary tumour location No. (percent)	Head and neck	47 (20.61%)	11 (11.34%)	0.119
	Trunk	82 (35.96%)	46 (47.42%)	
	Upper extremity	44 (19.30%)	16 (16.49%)	
	Lower extremity	55 (24.12%)	24 (24.74%)	
Tumour type No. (percent)	Nodular melanoma	148 (64.91%)	74 (76.29%)	0.190
	Superficial spreading melanoma	52 (22.81%)	16 (16.49%)	
	Acral lentiginous melanoma	9 (3.95%)	5 (5.15%)	
	Lentigo maligna melanoma	7 (3.07%)	0 (0.00%)	
	Desmoplastic melanoma	7 (3.07%)	1 (1.03%)	
	Amelanotic melanoma	5 (2.19%)	1 (1.03%)	
Positive sentinel lymph node biopsy	No. of positive result (percent)	68 (29.82%)	38 (39.17%)	0.121
Ulceration	No. of positive result (percent)	108 (47.37%)	32 (32.98%)	0.020

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272 **TABLE 2.** Study patients' follow-up characteristics

Characteristics	Margin of surgery		Exact Sig. (2-sided)
	1 cm	2 cm	
Local recurrence, (percent)	7(3.07%)	4(4.12%)	0.739
Locoregional metastases, (percent)	48(21.05%)	26(26.80%)	0.311
Distant metastases, (percent)	52 (22.81%)	25 (25.77%)	0.571
Death attributed to melanoma, (percent)	36 (15.79%)	18 (18.56%)	0.625

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276 **TABLE 3.** Means for disease free survival and overall survival Time

Margin	Mean ^a for DFS Time				Means for OS Time			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
1cm	3289.17	157.72	2980.03	3598.31	4150.41	125.75	3903.94	4396.89
2cm	2139.09	110.38	1922.76	2355.43	2551.48	76.19	2402.134	2700.82
Overall	3253.04	135.34	2987.78	3518.30	4085.29	111.62	3866.50	4304.07

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