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**Management of primary and metastasized melanoma in  
Germany 1976–2005.**

**An analysis of the Central Malignant Melanoma  
Registry of the German Dermatological Society.**

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To my parents

## Table of content

1	Introduction .....	1
2	Patients and Methods.....	3
2.1	Patients .....	3
2.2	Statistical analysis.....	4
3	Results .....	5
3.1	Clinical Characteristics–primary melanoma (Table 1) .....	5
3.2	Management of primary melanoma.....	5
3.2.1	Excision margins (Figure 1a-e) .....	5
3.2.2	One step vs. two step excision (Figure 2a-c) .....	6
3.3	Management of metastasized melanoma (Table 2) .....	7
4	Discussion.....	8
4.1	Clinical Characteristics.....	8
4.2	Excision margins .....	8
4.3	One step vs. two step excision.....	9
4.4	Management of metastasized melanoma .....	11
4.5	Limitations of the study .....	12
5	Conclusion .....	13
6	Figures and Tables .....	14
6.1	Figure 1 .....	14
6.2	Figure 2.....	17
6.3	Table 1 .....	19
6.4	Table 2.....	20
7	Legends to Figures and Tables.....	21
7.1	Figure 1 .....	21
7.2	Figure 2.....	22
7.3	Table 1 .....	23
7.4	Table 2.....	23
8	References.....	24

## 1 Introduction

Clark's and Breslow's pioneering definitions of level of invasion and tumour thickness in cutaneous melanoma (CM) formed the basic fundament for prospective randomised studies analysing the influence of excision margin on the prognosis of patients with cutaneous melanoma. In 1970 Breslow emphasized the importance of the vertical tumour thickness on prognosis and proposed that the size of the resection margin should be dependent on the tumour's anatomic location and thickness.<sup>1,2</sup> Further large randomised studies by Veronesi et al (1988) and Balch et al. (1993 and 2001) showed that smaller margins were adequate for the treatment of thin melanoma without any significant changes in the development of local recurrences, metastasized disease and the survival rate.<sup>3-5</sup> A need for wider excision margins was recommended for CM with a thickness of 4.0 mm and more<sup>6</sup> whereas stage I CM could be treated with a more conservative excision margin of 1.00 to 1.50 cm.<sup>7</sup> An analysis of Randomized Controlled Trials (RCTs) demonstrated no statistically significant difference in disease-free and overall survival between patients treated with wide or narrow excision margins.<sup>8</sup> A meta-analysis of three RCT and their follow-ups<sup>3,4,9-11</sup> revealed that an excision margin of 2 cm or less is adequate for surgery of primary CM without a negative affect on on local recurrences, disease-free and overall survival.<sup>12</sup>

On the basis of several randomised prospective studies<sup>3,5,7</sup> and results of international consensus conferences, the current German Guideline CM (2006) recommended reduced excision margins between 1,0 to 2,0 cm for the excision of stage I and stage II CM, according to the American Joint Committee on Cancer staging criteria (AJCC 2002).<sup>13,14</sup>

Planning surgical management implies the consideration whether excising in one session or choosing a two step approach. Two step surgery usually consists of an initial excision biopsy followed by definitive surgery with an excision margin.<sup>15</sup>

Therapy of metastasized melanoma is depending on the type and the occurrence of the metastases. Surgery forms the main treatment in metastasized melanoma as it holds multiple indications and provides the best prognosis whenever applicable. In case of coexistent distant metastases, systemic therapy can be taken into consideration. Radiotherapy has its main indication in extended inoperable metastases and effects more palliative treatment.<sup>16</sup> Indications for systemic therapy with mainly palliative aims are inoperable regional and distant metastases. As further knowledge has been obtained since the 1970s, treatment of metastasized melanoma changed explicitly during the last three decades.

The present study describes the development of the management of primary and metastasized melanoma in Germany between 1976 and 2005 as recorded by the German Central Malignant Melanoma Registry. The study focuses on changes of the excision margins in correlation with tumour thickness, surgical management in different geographical regions of Germany and treatment of metastasized melanoma.

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## 2 Patients and Methods

### 2.1 Patients

By December 2005 the German Central Malignant Melanoma Registry (CMMR) had recorded 69,420 patients with CM. Informed consent had been obtained from all patients. The data was collected from 79 clinical centres throughout Germany. The CMMR database is currently one of the largest CM databases world-wide and contains information about 35-50% of all melanoma patients in Germany.<sup>17</sup> The data of the CMMR is not population based. Nevertheless, the database can be considered as rather representative as a respective area is covered by one centre recording this region almost completely. Most CM patients are regularly transferred to dermatological centres participating in the CMMR.

As the study just analysed invasive primary CM, 7,438 in-situ lesions were excluded. Of the remaining 61,982 patients, 19,330 were excluded for the following reasons: missing information about excision margin (n=9,912), missing information about one or two step surgical management (n=306), missing information on tumour thickness or age (n=3,596), others than cutaneous melanomas (n=4,704) or melanoma of unknown primary (n=812). The present study finally included the data of 42,652 patients with invasive primary cutaneous melanoma recorded in the period between 1976 and 2005 in Germany.

The following information was recorded: age at diagnosis, gender, tumour thickness (in mm), histological subtype, level of invasion, excision margin (in cm), type of surgical management (one or two step) and geographical region in Germany (North, West, East, South). Body site was classified as head, scalp and neck, upper extremity, lower extremity and trunk.

The total collective of 42,652 patients contained information about 3,937 patients with 7,764 sites of metastases and about their treatments. In the

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CMMR a patient can be listed with several metastases. A total of 189 patients with 373 sites of metastases had to be excluded for missing data concerning the type or date of metastases. The sample being analysed for the management of metastasized melanoma consisted of 3,748 patients with 7,389 sites of metastases.

## **2.2 Statistical analysis**

Statistical analyses were conducted using the statistic software SPSS 11.5 (SPSS Inc., Chicago, IL, USA). Numerical variables were described by mean values and standard deviations (SD) or median values and inter-quartile ranges (IQR) depending on their distributions.

Chi-square tests for trend were used to judge the relationship between excision margin (categorised to 0.1 – 0.99 cm, 1.0 – 1.99 cm, 2.0 – 2.99 cm, 3.0 – 3.99 cm, 4.0 – 4.99 cm, 5.0 cm and more) and time periods stratified by tumour thickness (categorised to  $\leq 1.00$  mm, 1.01-2.00mm, 2.01 – 4.00mm,  $>4.00$ mm).

Multiple linear regression analysis was used to judge the relationship between year of diagnosis and excision margin, adjusted for tumour thickness. Exact chi-square tests for trend were applied to judge the time trends of the therapeutical managements of metastasized melanoma.



## 3 Results

### 3.1 *Clinical Characteristics—primary melanoma (Table 1)*

The sample (n=42,652) consisted of 45.9% male patients, the mean age at diagnosis was 54.58 years (SD  $\pm$  16.17). The mean tumour thickness was 1.59 mm (SD  $\pm$  2.16), the median tumour thickness was for 0.9 mm (IQR 0.50, 1.90). Based on the geographical regions 18.7% of patients were registered from northern Germany, 22.1% from western Germany, 34.1% from southern Germany and 25.1% from Eastern Germany.

### 3.2 *Management of primary melanoma*

#### 3.2.1 *Excision margins (Figure 1a-e)*

The total collective showed large excision margins of 5.00 cm and more (57.8%) predominantly used in 1976-80, dropping rapidly to 29% in 1981-85 and further to 0.2% in 2001-05. The number of excisions using excision margins of 3.00 to 3.99 cm increased continuously between 1976 and 1990 from initially 18.8% up to 46.4% but decreased to 6.6% until 2005. In contrast, excision margins of 1.00 to 1.99 cm were used in 6.9% of excisions in 1976-1980 and reached 60.2% in the time period 2001-05 ( $p < 0.0001$ ). This development of excision margins 1.00 to 1.99 cm over 30 years is distinguished by the trend line ( $p < 0.0001$ ), Figure 1a.

In CM with up to 1.00 mm tumour thickness, excision margins of 5.00 cm and more were predominantly used in the time period 1976-80 (56.8%), while in 1986-90 the majority of surgeries adopted 3.00 to 3.99 cm (43.0%) excision margins. Since 1991-95 these margins were reduced to 1.00 to 1.99 cm accounting for 83.1% in 2001-05, Figure 1b.

In the tumour thickness category of 1.01–2.00 mm similar trends could be observed (Figure 1c). Excisions dealing with CM thicker than 2.00 mm showed comparable tendencies to those dealing with 1.01-2.00 mm ( $P < 0.0001$ ) although excision margins of 2.00-2.99 cm prevailed for longer, Figure 1d. Overall, excision margins decreased significantly between 1976 and 2005 ( $p < 0.0001$ ). Median excision margin decreased from 5 cm (IQR = 3.0, 5.0; (mean=4 cm; SD=1.37) in 1976-80 to 1 cm (IQR = 1.0, 2.0; mean=1.4 cm; SD=0.66) in 2001-2005. This time trend remained significant after adjustment for tumour thickness ( $P < 0.0001$ ). The changes of median excision margins according to tumour thickness are shown in Figure 1e.

### **3.2.2 One step vs. two step excision (Figure 2a-c)**

One step excision dominated (~60%) surgical management during the years 1976 to 1985, two step excision increased constantly since then and is now performed in the majority of cases (75.8%) ( $p < 0.0001$ ), Figure 2a. No significant discrepancies were identified in excision patterns between Northern, Western and Southern Germany (Figure 2b), where two step surgery prevailed. The findings were different for the former German Democratic Republic, where most (53.9%) excisions were one step surgeries ( $p < 0.0001$ ). Regarding the changes in Eastern Germany during the last three decades, one step surgery dominated clearly in the beginning with average rates of 83.6% in the 1980s, starting to be replaced by two step surgery since 1996 ( $p < 0.0001$ ), Figure 2c.

### **3.3 Management of metastasized melanoma (Table 2)**

The collective being analysed for this specific question consisted of 3,937 patients with 7,389 sites of metastases. The results for the time period 1976 to 1980 were excluded from the statistical comparisons, as only 95 metastases were recorded during this period (1.3% of the total 7,389).

Regarding satellite and intransit metastases, surgery was and still is forming the major part of treatment with average rates of 80.6% across the thirty years of observation, although there was a tendency to lower frequencies ( $p = 0.004$ ). Systemic therapy dropped from 44.1% in the time period 1981 to 1985 to 20.7% in 2001 to 2005 ( $p < 0.001$ ), Table 2.

Similar tendencies in treatment of regional lymph node metastases were seen. Surgical treatment while dominating the treatment of regional lymph node metastases decreased in frequency during the three decades observed ( $p < 0.001$ ). Though decreasing significantly from 58.3% in the time period 1981 to 1985 to 27.4% in 2001 to 2005 ( $p < 0.001$ ), systemic therapy still formed the second most frequently used treatment, Table 2.

Distant metastases were predominantly treated with systemic chemotherapy, increasing from 30.6% in the time period 1981 to 1985 to 46.4% in 2001 to 2005 ( $p < 0.001$ ). Surgical treatment with an average rate of 15.4% across the three decades of observation was more prevalent than radio therapy with an average rate of 10.5%. 'No therapy' decreased significantly in extended disease from 23.0% in the time period 1981 to 1985 to 6.2% in 2001 to 2005 ( $p < 0.0001$ ).

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## 4 Discussion

### 4.1 *Clinical Characteristics*

The results of the present study, based on the data of 42,652 patients with incident cutaneous melanoma and consistent information on surgical management and excision margins, demonstrate the management of primary and metastasized melanoma in Germany 1976–2005. The sample consisted of 45.9% male patients with a mean age at diagnosis of 54.58 years and a mean tumour thickness of 1.59 mm.

The analysis concerning the management of metastasized melanoma contained a conspicuously smaller collective of data as only 3,748 patients with 7,389 sites of metastases including their treatment were recorded.

### 4.2 *Excision margins*

The discussion about a reduction of excision margins was prefaced in the 1980s. During the 1970s and in the beginning of the 1980s, CM were usually excised with a excision margin of 5 cm.<sup>18</sup> Several authors suggested that a reduction of excision margin to 3 cm would not affect the survival-rate negatively.<sup>19-22</sup> A large randomised study by Veronesi et al 1993 showed that the prognosis for CM with a tumour thickness up to 1 mm was not affected by a reduction of the excision margin to 1 cm.<sup>3</sup> Further studies by Balch et al 1993 and 2001 demonstrated no significant differences of survival rates for 2 or 4 cm excision margins in tumour ranging between 1 and 4 mm thickness.<sup>5</sup> In addition, Ringborg et al showed in 1996 that tumours of a thickness of 0.8 to 2.0 mm excised with margins 2 to 5 cm did not show any significant difference concerning the survival rate and the number of metastases.<sup>9</sup> These results led many clinical centres to favour smaller excision margins.

The present study analysed the development of excision margins over three decades in Germany and showed that excision margins decreased markedly. This analysis reveals how slow the conversion of significant results into clinical practice can be. Veronesi's results published in the late 1980s, clearly showed that the prognosis for CM with a tumour thickness of up to 1 mm is not altered by a reduction of the excision margin to 1 cm.<sup>3</sup> Nevertheless the process of cognition and realisation took one decade to prevail and discrepancies seem to be still remaining. In the time period 1991 to 1995, 50.1% of tumours of up to 1 mm in thickness were excised with margins less than 2.0 cm, in 1996-2000 this rate accounted for 74.1% and increased to 91.4% in 2001 to 2005. Note that in the time period 2001 to 2005 there were still 8.8% of tumours up to 1 mm in thickness being excised with margins equal or greater than 2.0 cm. This could be explained by several practices not being up to the actual state of affairs. The current German guidelines 2006, updated according to the American Joint Committee on Cancer staging criteria (AJCC 2002),<sup>13,14</sup> recommended a decrease of safety margins from 3 cm in 1994 and 2-3 cm in 1998 to 2 cm in 2005 in tumours >2 mm.<sup>23,24</sup> Consensus conferences of the NIH 1992 and the Dutch Melanoma Working Party 1992 and the 2005 update of the French guidelines show reductions of safety margins in the last years.<sup>25-27</sup> Possible aberrances in excision margins smaller than recommended could be caused by excisions in acral or facial localisations, where extended surgical intervention is impossible to fulfil.

### ***4.3 One step vs. two step excision***

The present study showed a constant increase in two step surgical management in Germany. According to the German guidelines punch biopsies are not performed in melanoma diagnosis and therefore this procedure is not taken into account in the assessment of one-step and two-step surgical procedures. This is true for Western, Southern and Northern Germany, however in the Eastern parts one step surgical management dominated until 1995 and

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has presently still a rate of almost 40%. It could be speculated that treatment of melanoma in the former German Democratic Republic was exclusively in hospitals, as private practice was virtually non-existent. This centralised system obviously favoured the one step excision management and was probably more reluctant to implement changes and innovations. One-step excisions were reported to be more common in patients with poorer prognostic features and often excision margins were lower than those suggested by current guidelines.<sup>15</sup> A study showed that patient survival was statistically significantly better with the two-stage procedure, although the reasons for this remained unclear.<sup>15</sup> A further study reported patients with one-step excisions to develop local recurrences more frequently than those in multiple step excisions (4.2% vs. 1.0%).<sup>28</sup> One reason for the apparent advantages of two-stage excisions could be that one-step operations are more likely to result in inadequate excision margins. Using a two-step procedure with a previous excision biopsy allows re-excisions appropriately corresponding to tumour thickness. Besides the quality of the surgical intervention and factors like body site, tumour surface area and histological type, the parameters of level of invasion and particularly of tumour thickness are influencing the probability of local recurrences. However, local recurrences seem to be independent of excision margins as long as the recommendations on excision margins were respected.<sup>28</sup> Hence, one could argue that the number of two step surgeries could be reduced by using the adequate excision margin proposed for thin malignant melanomas and proposed for obviously thick tumours.<sup>29</sup> This approach could benefit both patients and health funds.

#### **4.4 Management of metastasized melanoma**

When initiating surgical treatment of metastasized melanoma it should be considered whether the aim is curative or palliative. The main condition for curative surgical success is the possibility of total resectability (R0 situation). The most favourable situation would be the existence of a metastasis in just one organ. In stage IV disease however, the treatment options are often predominantly palliative, implying an extension of survival time, preventing the progress of the disease or maintaining a certain quality of life. The mean survival rate for patients with distant metastases accounts for 7 to 9 months.<sup>30</sup> Surgical intervention is presently considered as the most effective therapy for metastasized melanoma in single or isolated distant metastases.<sup>31</sup> The concept of debulking, settled in between curative and palliative therapy, is evaluated critically as studies show only few positive results especially concerning the overall survival rate.

Similar to previous studies the present analysis also showed that surgery is forming the main therapy in intransit and satellite as well as in regional lymph node metastases, showing smaller percentages for distant metastases which are mainly treated systemically. The use of radio therapy in the treatment of metastasized disease reached a peak in the late 1980s and showed a stable frequency later on. As response rate did not improve, radio therapy in metastasized melanoma is restricted to special indications.<sup>13,32</sup> Systemic therapy is mainly used as a palliative part of treatment when surgical intervention is impossible and therefore is still the main treatment option in advanced disease.<sup>13</sup>

With the improvement of the medical health system, the 'no therapy' option decreased for all types of metastases, most obviously and here also significantly in extended disease, where it is decreasing from 41% in 1976 to 1980 to 6.2% in 2001 to 2005.

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### **4.5 *Limitations of the study***

The majority of patient data was recorded between 1986-1990 (27.0%) and 1996-2000 (28.8%). The time period between 2001 and 2005 is still in process to be documented retrospectively, and further data will be available. Only few patients were recorded between 1976 and 1980 (1.0%) and between 1981 and 1985 (5.1%). Therefore, the possibility of analysing this period is limited, especially for management of metastasized melanoma. Hence, the p-value calculation excluded the data recorded between 1976 and 1980. Up until recently cancer registration was very limited in Germany. Hence, the present data set although not population based provides the best and most representative information on cutaneous melanoma for German patients. It is one of the largest data sets for melanoma worldwide and allows trend analysis over decades.



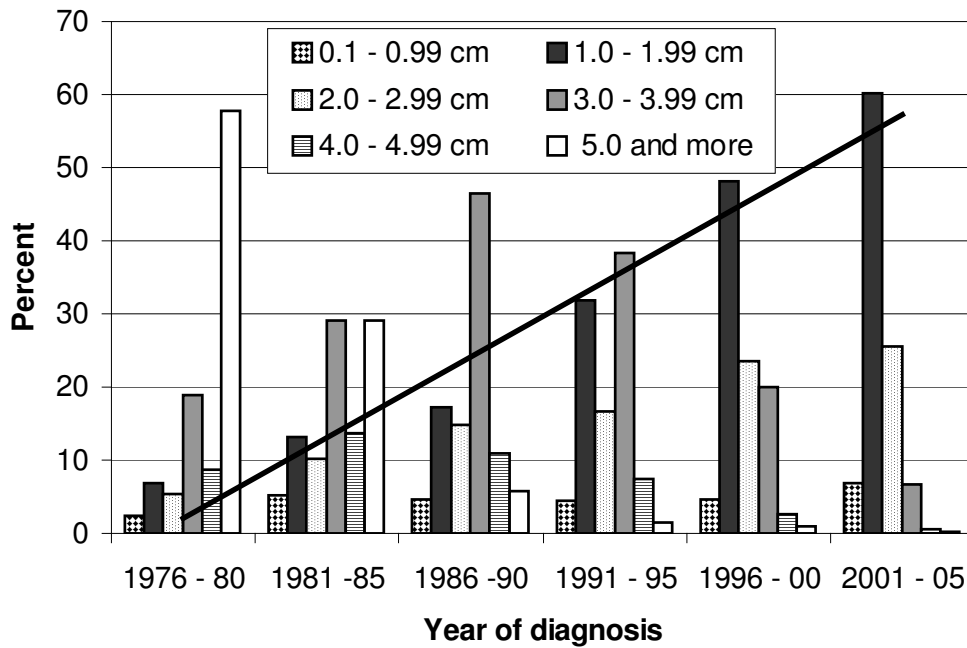
## 5 Conclusion

The present descriptive retrospective study revealed a significant time trend in excision margins to a maximum of 2.0 cm during the last three decades. The development of excision margins showed that large excision margins of 5.0 cm were predominantly used in 1976-80. They decreased rapidly to rates close zero in the recent time, being replaced by excision margins of 1.00 to 1.99 cm, which increased from 6.9% to 60.2% in the last 30 years. In primary CM a significant trend towards two step excisions was observed throughout Germany. Management of metastasized melanoma showed a propensity to surgical procedures in limited disease and an ongoing trend towards systemic treatment in advanced disease.

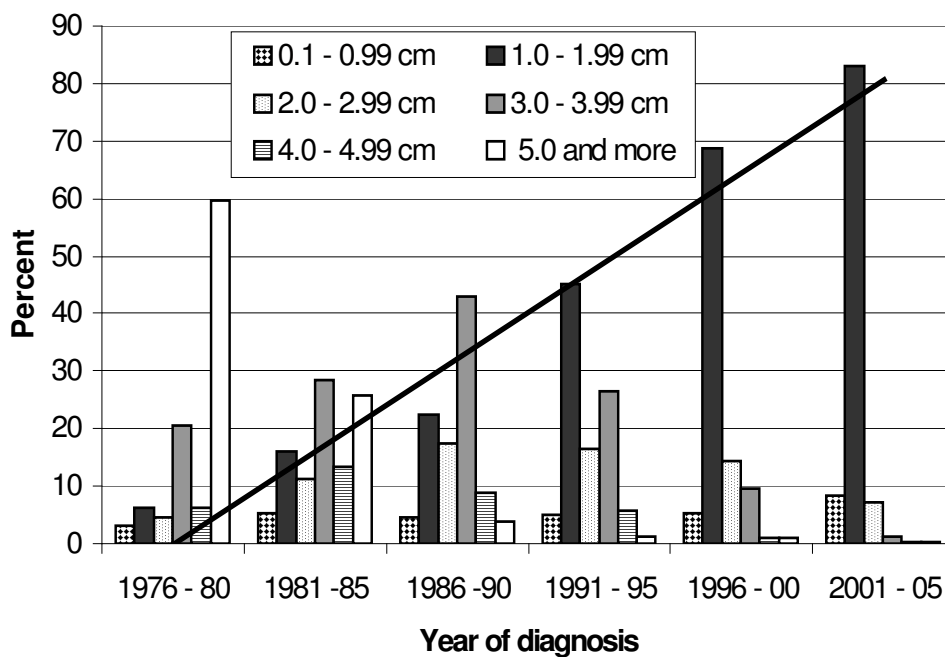
## 6 Figures and Tables

### 6.1 Figure 1

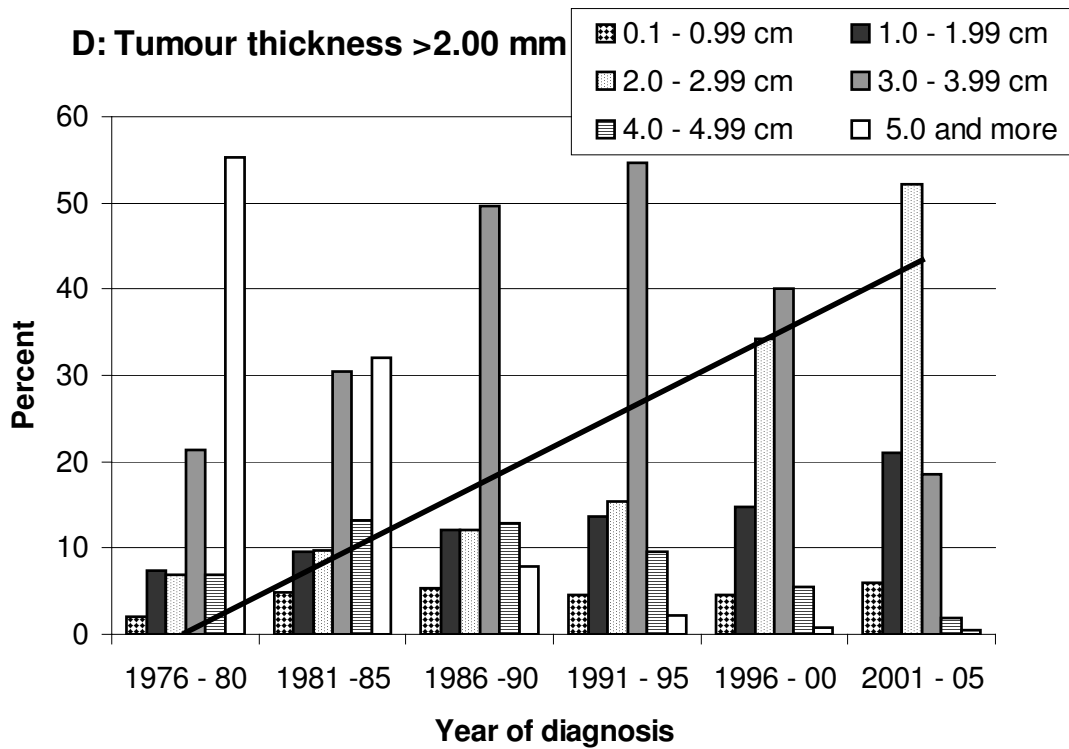
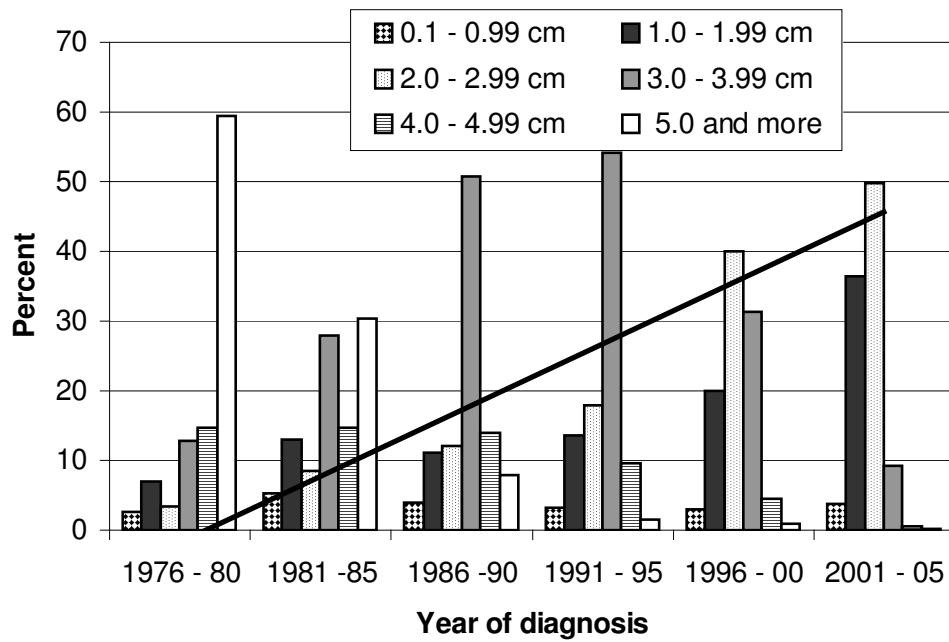
#### A: Total collective

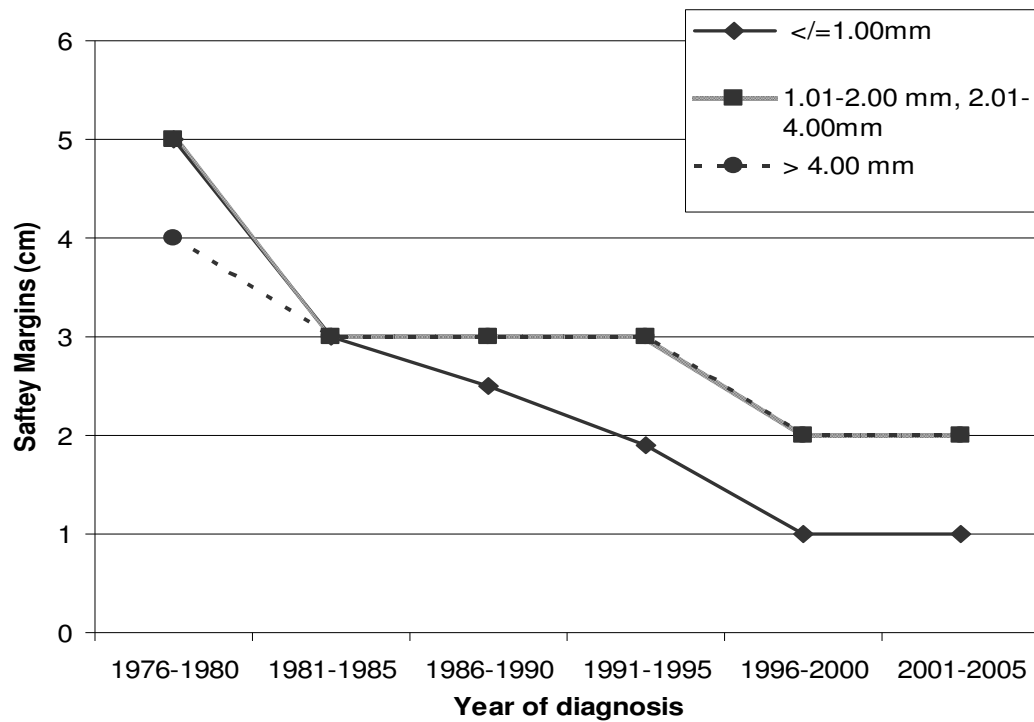
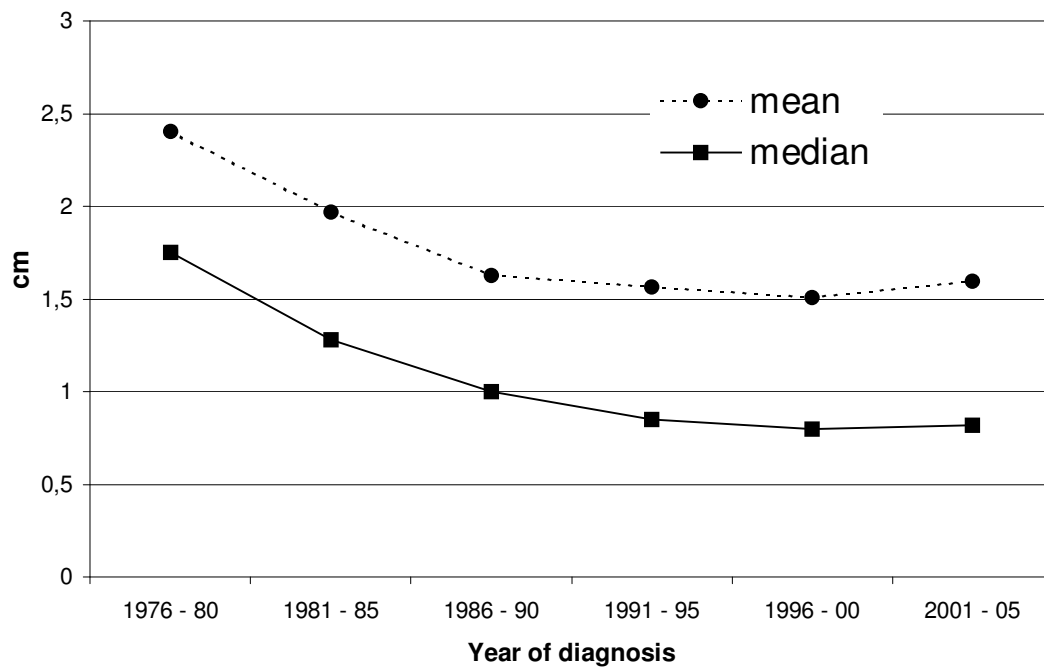


#### B: Tumour thickness up to 1.00 mm

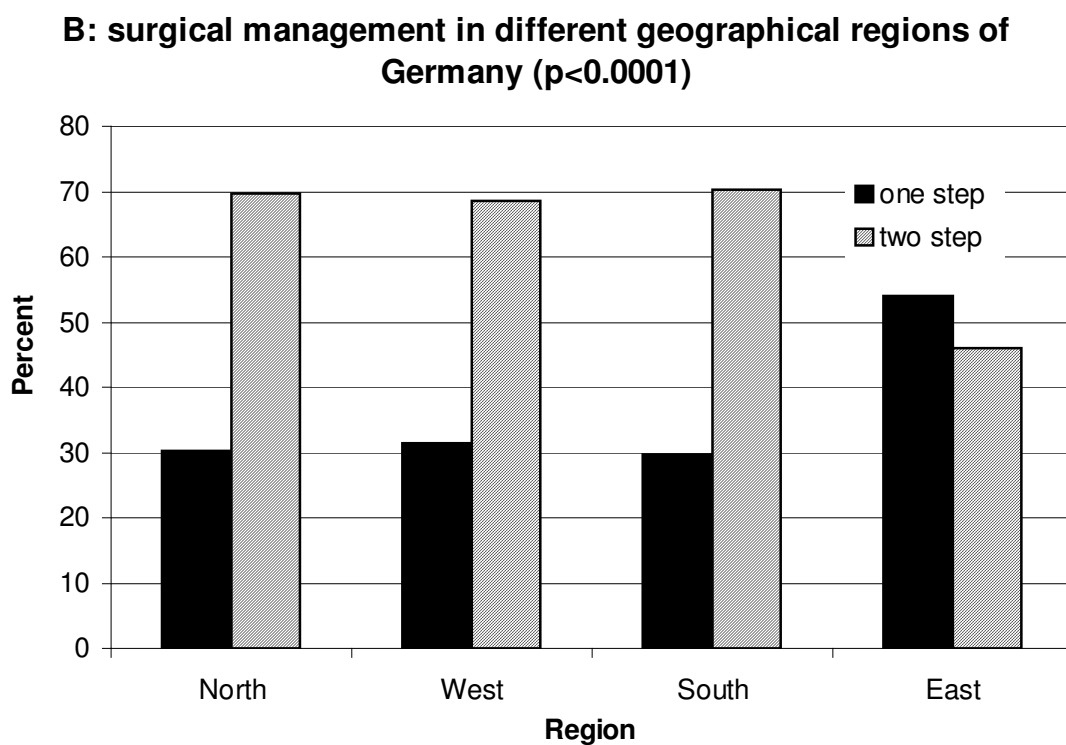
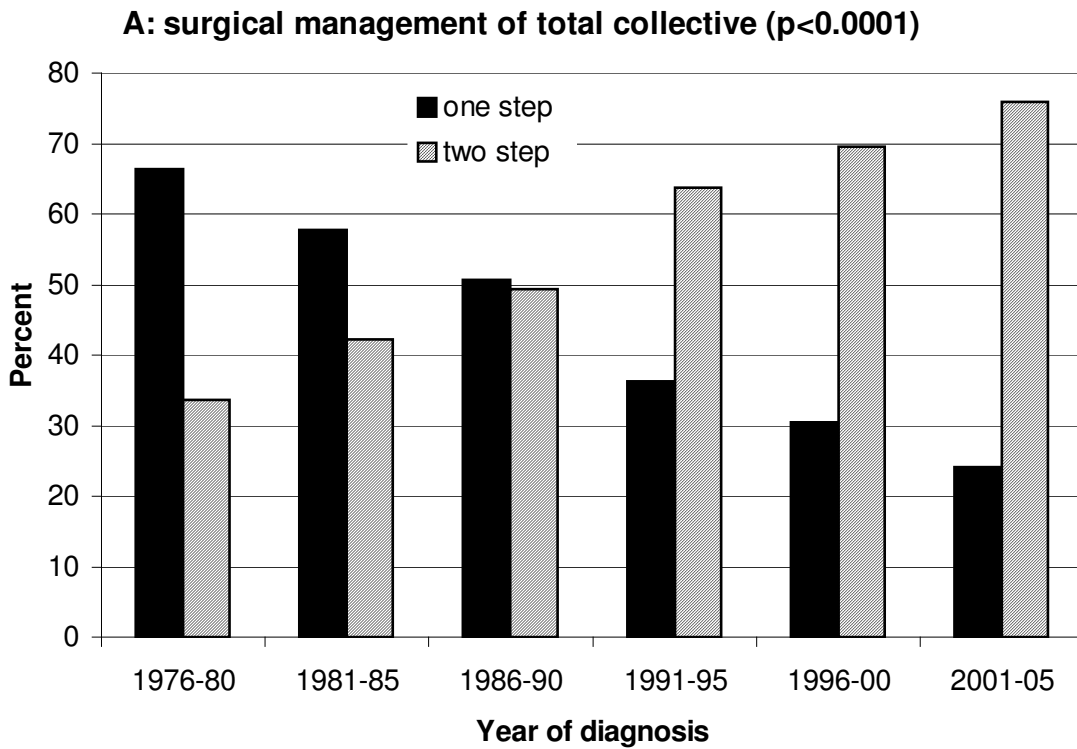


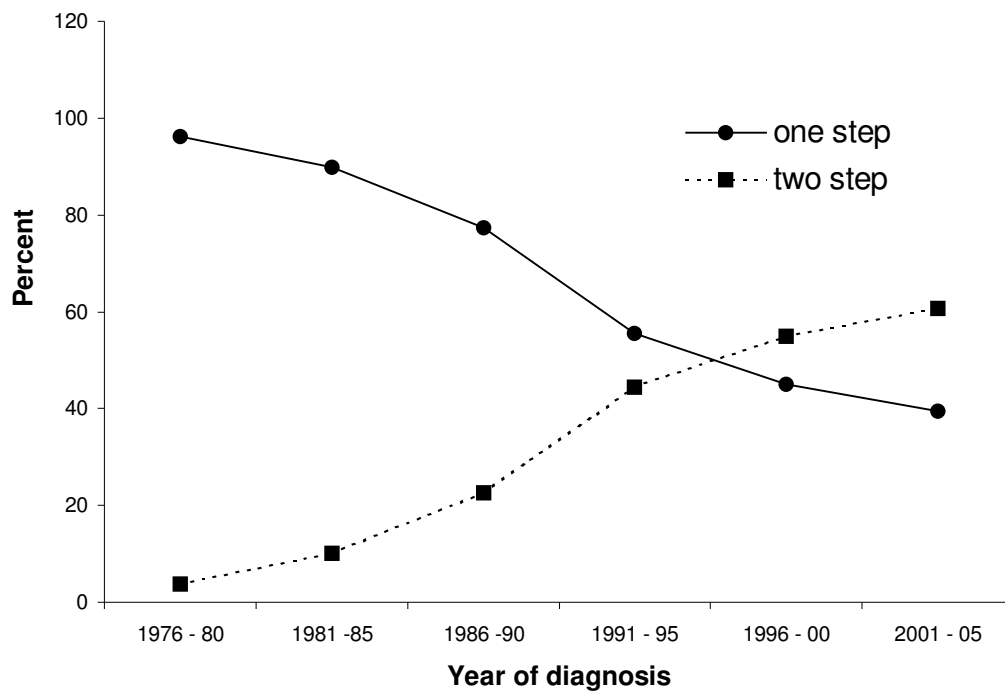
**C: Tumour thickness 1.01 - 2.00 mm**



**E: Median Safety Margins according to Tumour thickness****F: Time trends of mean and median tumour thickness**

## 6.2 Figure 2



**C: surgical management in Eastern Germany (p<0.0001)**

**6.3 Table 1**

<b>Prognostic factor</b>	<b>Distribution</b>
<b>Mean age at diagnosis (yrs) (<math>\pm</math> SD*)</b>	54.58 ( $\pm$ 16.17)
<b>Age (years)</b>	
$\leq$ 30	8.6%
31 – 40	13.0%
41 – 50	17.2%
51 – 60	22.3%
61 – 70	21.3%
71 – 80	13.5%
> 80	4.2%
<b>Gender</b>	
male	45.9%
female	54.1%
<b>Tumor thickness</b>	
<b>Mean (<math>\pm</math> SD), median (IQR**)</b>	1.59 mm ( $\pm$ 2.16), 0.9 mm (0.50, 1.90)
$\leq$ 1.00 mm	56.4%
1.01 – 2.00 mm	21.5%
2.01 – 4.00 mm	14.4%
> 4.00 mm	7.7%
<b>Level of invasion</b>	
II	22.8%
III	38.5%
IV	33.6%
..Missing values	n = 2173
<b>Histologic subtype***</b>	
SSM	61.3%
NM	18.2%
LMM	7.6%
ALM	3.3%
Others	9.6%
Missing values	n = 4076
<b>Body site</b>	
Head, scalp, and neck	12.6%
trunk	41.1%
Upper extremities	15.6%
Lower extremities	30.6%
Missing values	n = 44
<b>Year of diagnosis</b>	
1976 – 1980	1.0%
1981 – 1985	5.1%
1986 – 1990	19.0%
1991 – 1995	27.0%
1996 – 2000	28.8%
2001 – 2005	19.1%

**6.4 Table 2**

	1976 - 1980	1981 - 1985	1986 - 1990	1991 - 1995	1996 - 2000	2001 - 2005	p-values
<b>Satellite and intransit met.</b>	<b>Total: 16</b>	<b>136</b>	<b>348</b>	<b>535</b>	<b>426</b>	<b>372</b>	
Surgical treatment	12 75%	114 83.8%	292 83.9%	469 87.7%	314 73.7%	299 80.4%	0.501
Radiotherapy	1 6.3%	3 2.2%	27 7.8%	20 3.7%	19 4.5%	15 4.0%	0.045
Systemic therapy	10 62.5%	60 44.1%	100 28.7%	132 24.7%	113 26.5%	77 20.7%	0.003
Hyperthermic perfusion therapy	0 0.0%	8 5.9%	5 1.4%	12 2.2%	4 0.9%	4 1.1%	0.004
Other therapy	0 0.0%	2 1.5%	7 2.0%	16 3.0%	5 1.2%	19 5.1%	0.013
No therapy	1 6.3%	5 3.7%	10 2.9%	11 2.1%	8 1.9%	5 1.3%	0.474
<b>Regional lymphnode met.</b>	<b>Total: 40</b>	<b>163</b>	<b>491</b>	<b>718</b>	<b>725</b>	<b>456</b>	
Surgical treatment	29 72.5%	134 82.2%	405 82.5%	570 79.4%	518 71.4%	346 75.9%	0.469
Radiotherapy	2 5.0%	13 8.0%	44 9.0%	27 3.8%	33 4.6%	30 6.6%	0.003
Systemic therapy	24 60.0%	95 58.3%	177 36.0%	247 34.4%	253 34.9%	125 27.4%	0.000
Other therapy	0 0.0%	3 1.8%	17 3.5%	18 2.5%	10 1.4%	1 0.2%	0.005
No therapy	3 7.5%	8 4.9%	19 3.9%	33 4.6%	19 2.6%	15 3.3%	0.333
<b>Distant met.</b>	<b>Total: 39</b>	<b>209</b>	<b>434</b>	<b>759</b>	<b>861</b>	<b>661</b>	
Surgical treatment	2 5.1%	28 13.4%	79 18.2%	151 19.9%	152 17.7%	118 17.9%	0.480
Radiotherapy	2 5.1%	19 9.1%	68 15.7%	94 12.4%	80 9.3%	74 11.2%	0.033
Systemic therapy	11 28.2%	64 30.6%	144 33.2%	287 37.8%	364 42.3%	307 46.4%	0.009
Other therapy	0 0.0%	3 1.4%	13 3.0%	22 2.9%	4 0.5%	21 3.2%	0.001
No therapy	16 41.0%	48 23.0%	88 20.3%	116 15.3%	68 7.9%	41 6.2%	0.000



## 7 Legends to Figures and Tables

### 7.1 *Figure 1*

Time trends of safety margins according to tumour thickness classes, the p-value refers to the distribution over time.

**Figure 1a:** Trends show a significant increase to an excision margin of 1,00-1,99 mm in the total collective.

**Figure 1b:** In tumour thickness classes up to 1,00 mm a significant trend to an increase to an excision margin of 1,00-1,99 mm was found.

**Figure 1c:** In tumour thickness classes from 1,00 to 2,00 mm a significant trend to an increase to an excision margin of 2,0 – 2,99 mm was found.

**Figure 1d:** In tumour thickness classes of more than 2,00 mm a significant trend to an increase to an excision margin of 2,0 – 2,99 mm was found.

**Figure 1e:** Excision margins between 1976 and 2005 according to tumour thickness between 1976 and 2005.

**Figure 1f:** Time trends of mean and median tumour thickness between 1976 and 2005

## 7.2 *Figure 2*

Time trends of one and two step surgical management considered for the entire data set and stratified by geographical regions of Germany.

**Figure 2a:** Surgical management in total collective. A decrease in one step management and an increase in two step surgical management could be shown.

**Figure 2b:** Surgical management in different geographic regions. In eastern Germany one step surgical management was preferred.

**Figure 2c:** Time trends of surgical management in Eastern Germany. Before the 1990ies one step surgical management was predominantely performed in Eastern Germany, later a trend towards two step surgical management was performed.

### **7.3 Table 1**

Description of prognostic factors of incident primary cutaneous melanoma (n=42,625).

\* SD = Standard deviation, \*\* IQR = Inter-quartile range; \*\*\* SSM = superficial spreading melanoma, NM = nodular melanoma, LMM = lentigo maligna melanoma, ALM = acral lentiginous melanoma.

### **7.4 Table 2**

Treatments in metastasized melanoma.

Multiple responses were possible and rather frequent as many treatments consist of more than just one type of therapy.

The p-value calculations excluded the period between 1976 and 1980.

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## 8 References

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