Prognostic differences across sexes in melanoma patients: What has changed from the past?

Prognostic differences across sexes in melanoma patients: what has changed from the past?

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Abstract

Differences across the sexes include epidemiological trends, distribution of clinical features and prognostic relevance in melanoma patients. The aims of this singlei-nstitution hospital-based cohort study were as follows: to assess the trends over time of the male/female ratio; to analyse the clinicopathologic features according to sex and their modifications following the introduction in 1999 of sentinel lymph node biopsy; to ascertain the metastatic pathways across sexes and the prognostic role of sex in the disease-free interval (DFI), disease-specific survival (DSS) and survival after recurrence. The patient population included 4310 stage I–II melanoma patients, diagnosed, treated and followed up in our institution from 1975.

Patients were divided into two groups on the basis of the introduction of sentinel lymph node biopsy in 1999. A female prevalence was observed until 1999; thereafter, the male/female ratio approached 1 (period 1999–2003), with a subsequent increasing trend suggesting a potential male prevalence. Longer DFI and DSS were observed after 1999 and men showed greater improvement compared with women. In multivariate analyses, sex showed a lower impact on DFI and survival after recurrence following the introduction on sentinel lymph node biopsy. No sex-related differences in terms of DSS were observed before and after 1999 among patients with melanoma located on the trunk.

However, among patients with primary lesions not located on the trunk, sex maintained a significant prognostic role in both groups. The results of this study suggest that in the last few years, the prognosis of men could have improved more than that in women. The changing surgical/therapeutic interventions can influence sex disparities in melanoma.

Introduction

In Europe, the incidence of cutaneous melanoma (CM) is higher in women than in men, but this trend is opposite in the USA and in Australia [1–4]. In Italy, recent epidemiological data confirmed higher prevalence in women (CM represents 2.1% of all cancer diagnoses among women and 1.6% among men [5]) and a higher incidence in northern and central regions of the country [6]. A marked increase in thinner melanoma diagnoses has been observed in recent decades [7,8]; this is because of both the prevention campaigns and the improvement in diagnostic accuracy. The status of sentinel lymph node has been identified as a strong prognostic factor for survival and recurrence and the American Joint Committee on Cancer (AJCC) included it in the latest staging system for CM. Indeed, this procedure enables correct classification of T1–T4b/N0 melanoma patients and an anticipation of stage III, defining the correct diagnosis ab initio of patients classified previously as stage II, but who rapidly developed clinically evident nodal progression.

It has been established that men have a worse outcome than women. A different distribution of prognostic relevant clinical features was described across sexes: male patients are usually older and show

predominant axial localization, whereas the leg is a more common site in women [2,9]. However, sex also showed an independent prognostic role [10,11].
The objective of this study was to assess the changes over time in the male to female ratio, as well as the distribution of the different clinicopathological features according to sex, and their potential modifications consequent to the introduction of sentinel lymph node biopsy (SLNB). A second aim was to ascertain the differences in metastatic pathways and clinical outcome in terms of the disease-free interval (DFI), survival after recurrence (SAR) and disease-specific survival (DSS) across sexes before and after the introduction of SLNB.

Materials and methods

Patients

The clinical records of 5879 melanoma patients who were diagnosed and prospectively followed up at our Institution from 1975 to 2011 were reviewed and reclassified according to the new AJCC staging system [10].
Patients with incomplete histopathological data, noncutaneous or unknown primary melanoma, stage III and IV AJCC at diagnosis and with a follow-up of less than 1 year were excluded, thus leading to a total of 4310 patients with I–II AJCC stage [10].
The variables recorded were sex, age, years of diagnosis, site of primary melanoma, Breslow thickness, Clark level, histological type, ulceration, presence of multiple primary melanoma (MPM), site and type of progression. Regression was recorded and analysed only for the 2161 patients with diagnosis after 1 January 1999 because data collected before were incomplete. SLNB has been introduced since January 1999 in our Institution. SLNB inclusion criteria have been reported previously [12]. On the basis of SLNB introduction, patients were divided into two groups (group A diagnosed between 1975 and December 1998; group B diagnosed after January 1999).
Clinical and imaging follow-up was performed according to the guidelines reported previously [13–16]. Briefly, physical examinations were performed every 2–6 months on the basis of the Breslow thickness until 10 years from melanoma excision, and then yearly. Radiological imaging was performed at diagnosis and every 6–12 months during follow-up.
The first site of progression was defined as regional or distant. Regional involvement was categorized into three subgroups: (a) only skin, (b) only lymph nodes and (c) both skin and lymph nodes. Distant progressions were divided into three subgroups: (a) skin and/or lymph nodes, (b) only visceral involvement and (c) both visceral and skin/lymph nodes.

Statistical analysis

Statistical analyses were carried out using the Stata 12.0 Statistical Software (StataCorp LP, Texas, USA). Pearson's $\chi 2$-test and t-test were performed initially to evaluate potential differences in the distribution of variables between groups A and B.
For 4310 patients (in-situ melanoma were excluded by survival analyses), DFI was calculated from the surgical excision of primary melanoma to the date of first disease relapse or last check-up; SAR was calculated from the date of first disease relapse to the date of death or last check-up; and DSS was calculated from the surgical excision of primary melanoma to the date of melanoma death or last check-up. For the assessment of DFI, SAR and DSS, only death because of melanoma was considered as an event. Patients who had died from non-melanoma related causes were monitored until the last available follow-up visit.
Survival estimates were derived using the Kaplan–Meier method and the statistical comparisons were performed using the log-rank test. Univariate Cox regression analyses were carried out on DFI, SAR and DSS to evaluate the role of sex, age at diagnosis, Breslow thickness, ulceration, histological type, presence of MPM, histological regression, site of primary and site of first relapse (only on SAR). These variables were then included in a multivariate Cox regression, except for histological regression, because complete data were available only after 1999.
The proportionality assumption was assessed by Schoenfeld residuals; whenever this assumption was not satisfied, separate proportional hazard models were run for each stratum of the violating covariate. The log-likelihoods ratio test was used to define linear or categorical nature of Breslow thickness. Sites of primary (six categories in our data collection, Table 1) were tested initially to assess the significant ones;

afterwards, foot and trunk sites were dichotomized versus the other localization combined. Histological type was dichotomized and age at diagnosis was assumed to be continuous. Akaike Information Criterion was used to select the model in terms of number of variables included and yields the best outcome.

Results

Trends in sex distribution over the years.

The study cohort included 4879 patients: 2686 (55%) women and 2193 (45%) men (overall male/female ratio 0.82). A different trend in sex distribution was observed according to the time period of diagnosis. The male/female ratio ranged from 0.62 to 0.78 until 1999. In the period 1999–2003, the ratio became 1, whereas in the period 2004–2008, a predominance of male patients was observed (ratio 1.19). As a consequence, women were significantly more highly represented only among the patients diagnosed before 1999 (59.3%).

Clinical–pathologic features of patients of group A and B

Patients were divided into two groups (groups A and B) with a cut-off fixed in January 1999 on the basis of the introduction of SLNB in our department. Moreover, in the time period 1999–2003, a balance between new diagnoses was observed between men and women. A significantly higher number of in-situ melanomas were observed in group B (467 cases; 198 men and 269 women) than in group A (102 cases; 34 men and 68 women).

The distribution of clinical–pathologic parameters in the two groups is shown in Table 1 (in-situ melanoma excluded). In group A, the proportion of stage II compared with stage I patients was significantly higher among men than women. Afterwards, stage II diagnoses decreased without differences across sexes. In group B, men were significantly older than women.

Men developed MPM more frequently in both time periods. Breslow thickness decreased in both sexes, and women maintained lower mean values. Ulceration was present in both groups, with a higher frequency in men (A: 15.7 vs. 11.3%; B: 19.9 vs. 16.2%). Nodular melanomas (NMs) were significantly more frequent in group A, with a higher male predominance than in group B.

Patterns of progressions

Before the introduction of SLNB, 36.1% of the patients developed disease progression, and only 20.5% after the introduction of SLNB ($P< 0.001$). The first progression occurred more frequently in the regional site in both groups (79.2% in group A and 64.5% in group B). However, after the introduction of SLNB, a relative increase in distant metastases was observed (20.8% in group A and 35.4% in group B). The reduction in regional metastases in group B was mainly because of a reduction in regional node involvement (71.5 vs. 58.9%). Interestingly, in this group, we observed significantly higher number of skin regional progression in women compared with men (38.0 vs. 18.5%). Before the introduction of SLNB, there was no sex-related difference in the frequency of first progression in a distant site; however, this event was more frequent in men in group B. Moreover, when we considered group A and group B together, multiple visceral sites occurred, as first recurrence, predominantly in men (39.8%) than women (23%) ($P =0.05$) (Table 1).

DFI, SAR and DSS analyses in groups A and B

Separate analyses were carried out to evaluate the prognostic parameters for DFI, SAR and DSS in patients in groups A and B. The patients in group B showed significantly longer DFI and DSS compared with those in group A (Table 1). Even though this improvement was greater in men, they still maintained a disadvantage in terms of DFI and DSS compared with women (Fig. 1a–f). We did not find any differences in SAR for women on comparing the two groups ($P =0.57$), but interestingly, men had a shorter SAR in group B ($P= 0.029$).

Univariate analyses confirmed sex as a significant prognostic factor for DFI, SAR and DSS in both groups (Table 2). Other significant prognostic factors common to both groups were age, Breslow thickness, ulceration, foot localization, MPM and NM histotype. However, trunk localization was significantly related to SAR and DSS only in group A.

Histological regression was performed only in group B, where it maintained an independent favourable role at univariate analysis on DSS, DFI and SAR. As regression was not available for the patients in group A, it was excluded from further multivariate analyses. However, also when added to the model, it maintained its protective prognostic role in DSS and DFI [DSS: hazard ratio (HR) 0.42, confidence interval (CI) 0.22–0.78; DFI: HR 0.62, CI 0.42–0.89; SAR: HR 0.65, CI 0.34–1.22], but did markedly.

In multivariate analyses of DFI and SAR, the proportionality assumption was satisfied. Male sex showed an independent unfavourable prognostic relevance in terms of DFI and SAR in group A, but not in group B (Tables 3 and 4). Age, Breslow thickness and ulceration maintained a negative role in DFI in both groups (Table 3). Furthermore, in group A, there was evidence of a negative role of trunk, foot localization and NM histotype and a positive role of MPM in DFI. The most important prognostic factor for the SAR was the site of first relapse in both groups; the only other variable significant was trunk localization (Table 4).
In multivariate analyses on DSS, the proportionality assumption was not satisfied (P= 0.002) and the goodness-of-fit was satisfied in group B, whereas the trunk covariate violated the proportional hazard assumption in group A (P = 0.002). Therefore, two multivariate Cox regression models on the basis of trunk site were constructed (Table 5).
Sex had a significant influence on DSS in both time periods for patients with melanoma not located on the trunk. Interestingly, a different pattern of progression was observed across sexes in both time periods. Lymph node involvement was the most frequent site of progression in both sexes and in both groups, but in men, we observed a higher percentage of distant metastases and a lower percentage of in-transit metastases compared with women in both time periods. Age, Breslow thickness and ulceration maintained a negative role in DSS in both groups, whereas MPM played a positive role in DSS only before the introduction of SLNB. There was no evidence of a role of NM in either group.
However, in patients with primary melanoma on the trunk, there was no evidence of an effect of sex on time to DSS in both time periods and no difference in the pattern of progression was observed across the sexes. In group A, an independent role was maintained by Breslow thickness, ulceration and MPM, whereas in group B, ulceration lost significance.

Discussion

Sex is associated with relevant differences in melanoma patients from several points of view. First, from an epidemiological aspect, figures from the USA and Australia show a male prevalence, whereas in European countries, the incidence in men has been lower in the past few years and recently reached the same values [1–3]. Sex is associated with a different distribution of clinical features and could play a role as a prognostic indicator, although it is not included in the AJCC classification. Women have a prognostic advantage compared with men, but the reasons for this disparity have not been identified as yet.
Many hypotheses have been proposed: hormonal influences [17], differences in sun exposure habits [18], lower awareness and resistance to screening among men [19]. Recently, this topic has been explored in more depth and new analyses have been published [3,4,20 –23]. However, none of these estimated the impact of the introduction of SLNB on sex prognosis. This evidence led us to carry out a study on a single-institution hospital-based cohort of 4879 CM consecutive patients diagnosed, treated and followed up from 1975 to 2011.
The first finding of our study is a different trend in the epidemiological distribution of melanoma patients. In the past few years, CM was considered a disease that was more frequent in women in the European countries. In contrast, we observed a male/female ratio of one in the time period 1999–2003; afterwards, we observed increased new diagnoses in men, suggesting a potentially higher prevalence of melanoma in men. These results were obtained from a single-institution hospital, but our Melanoma Unit is the reference centre of the region.
Moreover, we found the same trend in the official tumour registry of the region. From 1999, male incidence started to increase and after 2007 it overcame the female incidence [24]. Recently, the Munich Melanoma Group reported a similar distribution between sexes in a registry-based study [25]. Therefore, it seems conceivable that the sex distribution of melanoma is changing.
This could be because of differences in sun exposure habits [18] and a higher awareness of the importance of skin surveillance in men. Men may have benefited more from the prevention campaigns conducted in the past few years in our country. This screening tool also resulted in an increase in in situ and thinner melanoma in both sexes. SLNB was introduced in our Department in 1999; with this cut-off, we divided patients into two groups: (a) group A patients diagnosed before 1999 and (b) group B patients diagnosed after 1 January 1999. A significant reduction in Breslow thickness and a consequent reduction in disease progression were observed in group B. The progression rate decreased from 36.1% before 1999 to 20.5% after 1999. This survival benefit may have been derived from an improvement in early diagnosis, but could

also be related to the type of population included in this analysis and the different follow-up durations of the two cohorts, which could have underestimated the progression, especially in group B. Indeed, we carried out our study in stage I or II patients and it should be kept in mind that since the introduction of SLNB, the stage classification of patients has changed.

This procedure allows a correct diagnosis ab initio, with an early detection of stage III patients who previously would have been classified as stage I or II, but would have experienced clinically evident nodal progression rapidly. A positive SLNB and consequent stage III at diagnosis are more frequent in men [12,26,27]; this supports the relative reduction in stage II male patients in group B. Before the introduction of SLNB, we found [23,28] a higher percentage of skin involvement in women, whereas nodal progression was higher in men. This different pattern of progression could in part explain the better prognosis of women in this group of patients. After the introduction of SLNB, we observed a relative increase in first progression in a distant site in both sexes (35.5 vs. 20.7%). This phenomenon was more frequent in men (P =0.002), perhaps because of the association of male sex with several unfavourable prognostic factors such as higher Breslow thickness, more frequent ulceration, older age and predominant axial site distribution.

Our observation confirmed the findings already reported by Mervic [23]; in her case series, distant metastases were also more frequent in men than in women.

Other interesting findings were obtained from the survival analyses carried out on DFI, SAR and DSS. After the introduction of SLNB, the male sex lost its significant prognostic value in terms of both DFI and SAR when corrected for the other prognostic features.

As described previously [1,2,29] after the introduction of SLNB, the observed time to relapse was longer in both sexes; in our study, we also observed that this improvement was higher in men. The significant unfavourable role of the trunk location in DFI was maintained only in group A. Probably in group B, the trunk is no longer related to a shorter DFI because, as already described [12], most of the patients with a positive SLNB had a melanoma on the trunk (42%) and, as stage III, were excluded from our analysis. Thus, the patients with a trunk melanoma in group B are more frequently patients who will develop a visceral first progression, with a longer DFI. Multivariate analyses on DSS were stratified by trunk as this variable violated the proportional hazard assumption. These separate analyses showed that the introduction of SLNB did not influence sex-related differences in terms of DSS.

Recently, histological regression was associated with a better survival and it was also protective against sentinel lymph node metastases [27,30–33]. In our study, regression data were available only after 1999 and this parameter was evaluated only in univariate analyses. Nevertheless, regression was more frequently found in men and confirmed a protective role on DFI, DSS and SAR. Our recent published data supported this finding. We showed that regression should not be considered when performing SLNB in thin melanoma; in contrast, it can be considered a favourable prognostic factor in stage I–II AJCC patients [33].

The SAR showed an opposite trend compared with DFI and DSS, with a slight eduction in 5- and 10-year rates after 1999. This could appear controversial but after the introduction of SLNB, despite a reduction in the progression rate, we observed a marked relative increase in distant metastases, which led to a consequent shorter survival.

On univariate analyses, SAR in men appeared to be lower than in women, but on multivariate analyses, male sex lost its relevance in group B. After the introduction of SLNB, the only variables that maintained a significant prognostic role were a primary lesion located on the trunk and a recurrence in a distant site.

Breslow thickness and ulceration, the most recognized prognostic parameters in melanoma, showed a significant prognostic relevance on SAR only in univariate analysis.

On multivariate analyses, Breslow thickness maintained a borderline significant role only after 1999, and was not impacting SAR before, as reported previously by Mervic [23]. However, ulceration was a significant prognostic factor only before 1999.

To conclude, in this study, we have shown [1,2,29] an overall survival improvement from 1990s to date. In particular, prognosis in men, in term of DSS, seemed to be more favourable after the introduction of SLNB. Male sex maintained an unfavourably significant role only in patients with a primary lesion not located on the trunk. It could be interesting to evaluate whether a longer followup of patients diagnosed after 1999 could determine a further improvement in survival of male patients.

Moreover, after the introduction of SLNB, there were no differences across sexes in terms of DFI and SAR. These data suggest that the recent changes in surgical/therapeutic intervention, such as SLNB, could have a different impact across the sexes.

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Conflicts of interest There are no conflicts of interest.

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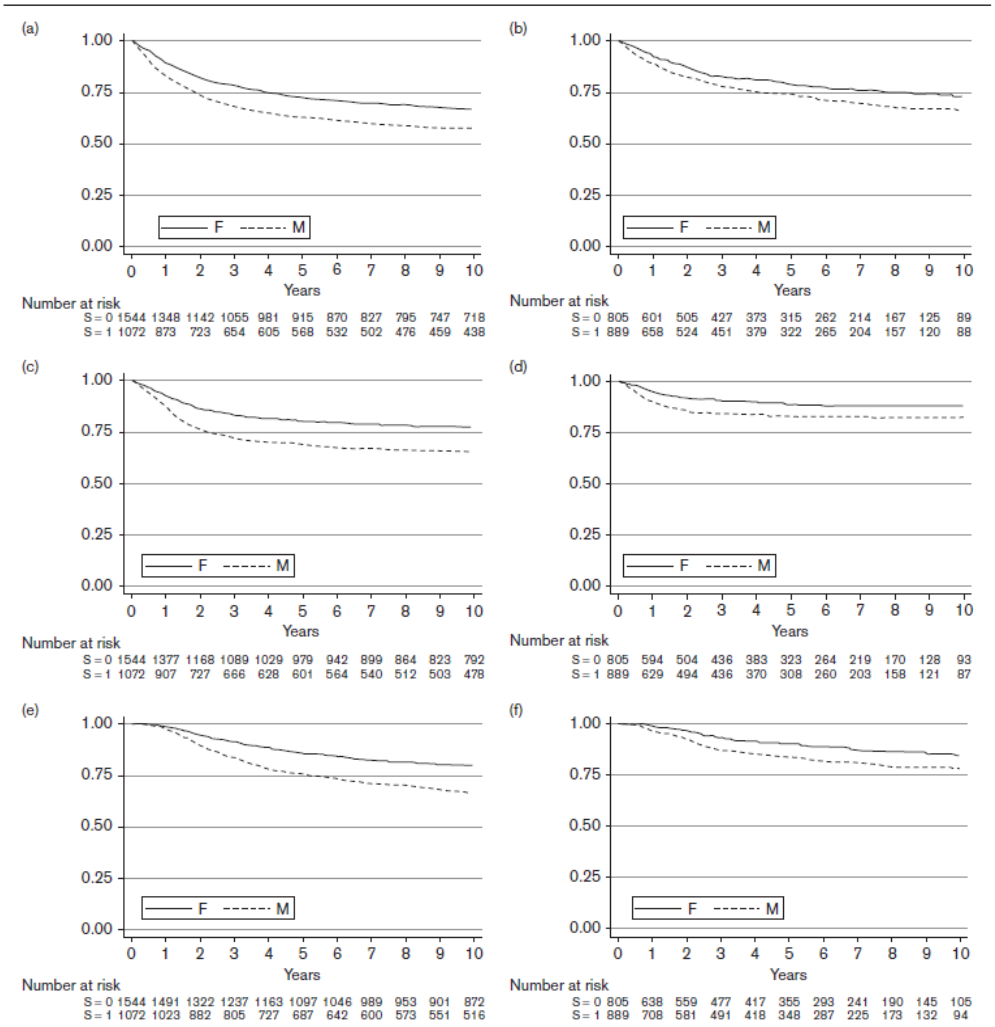
Table 1 Clinicopathological features before (group A) and after (group B) 1 January 1999 across the sexes

	Group A (1975–1998) [*n* (%)]			Group B (1999–2011) [*n* (%)]		
	Male	Female	*P*	Male	Female	*P*
Total	1072	1544		889	805	
Age						
Median	53 (18–91)	54 (10–93)	0.56	60 (7–90)	53 (11–90)	< 0.001
< 65	848 (79.1)	1170 (75.8)	0.04	549 (61.7)	566 (70.3)	< 0.001
≥ 65	224 (20.9)	374 (24.2)		340 (38.3)	239 (29.7)	
Site of primary melanoma						
Head/neck	139 (13.0)	223 (14.4)	< 0.001	96 (10.8)	63 (7.8)	< 0.001
Trunk	581 (54.2)	347 (22.5)		520 (58.5)	260 (32.3)	
Upper extremities	115 (10.7)	193 (12.5)		109 (12.2)	112 (13.9)	
Hand	9 (0.8)	28 (1.8)		6 (0.7)	6 (0.7)	
Lower extremities	156 (14.6)	609 (39.4)		126 (14.2)	305 (38.0)	
Foot	72 (6.7)	144 (9.3)		32 (3.6)	59 (7.3)	
MPM						
No	982 (91.6)	1448 (93.8)	0.03	795 (89.4)	745 (92.6)	0.02
Yes	90 (8.4)	96 (6.2)		94 (10.6)	60 (7.4)	
Breslow thickness						
≤ 1	337 (31.4)	618 (40.0)	< 0.001	417 (46.9)	427 (53.0)	0.002
1 < Br ≤ 2	285 (26.6)	385 (24.9)		166 (18.7)	139 (17.3)	
2 < Br ≤ 4	273 (25.5)	350 (22.7)		158 (17.8)	152 (18.9)	
Br > 4	177 (16.5)	191 (12.4)		148 (16.6)	87 (10.8)	
Histological type						
SSM	723 (67.4)	1019 (66.0)	0.011	687 (77.3)	624 (77.5)	0.708
NM	173 (16.1)	198 (12.8)		110 (12.4)	91 (11.3)	
ALM	58 (5.4)	107 (6.9)		29 (3.3)	36 (4.5)	
LMM	68 (6.3)	135 (8.7)		48 (5.4)	42 (5.2)	
Other	50 (4.7)	85 (5.5)		15 (1.7)	12 (1.5)	
Clark level						
II	174 (16.2)	344 (22.3)	0.002	164 (18.4)	213 (26.5)	< 0.001
III	699 (65.2)	922 (59.7)		418 (47.0)	325 (40.3)	
IV	172 (16.0)	234 (15.2)		263 (29.6)	238 (29.6)	
V	27 (2.5)	44 (2.8)		44 (5.0)	29 (3.6)	
Ulceration						
No	904 (84.3)	1370 (88.7)	0.001	712 (80.1)	675 (83.8)	0.04
Yes	168 (15.7)	174 (11.3)		177 (19.9)	130 (16.2)	
Histological regression[a]						
No				675 (75.9)	658 (81.7)	0.004
Yes				214 (24.1)	147 (18.3)	
AJCC stage						
I	603 (56.2)	983 (63.7)	< 0.001	564 (63.4)	544 (67.6)	0.083
II	469 (43.8)	561 (36.3)		325 (36.6)	261 (32.4)	
Ia	334 (31.2)	609 (39.4)	< 0.001	400 (45.0)	409 (50.8)	< 0.001
Ib	269 (25.1)	374 (24.2)		164 (18.4)	135 (16.8)	
IIa	229 (21.4)	299 (19.4)		117 (13.2)	118 (14.7)	
IIb	158 (14.7)	187 (12.1)		120 (13.5)	96 (11.9)	
IIc	82 (7.6)	75 (4.9)		88 (9.9)	47 (5.8)	
DSS (%)						
5 years	75.5	85.8	< 0.001	83.9	90.2	< 0.001
10 years	66.6	79.8		78.4	84.7	
DFI (%)						
5 years	62.8	72.4	< 0.001	74.2	78.6	0.004
10 years	57.5	67.1		66.6	73.0	
SAR (%)						
5 years	28.0	42.3	< 0.001	22.0	41.4	< 0.001
10 years	20.9	34.7		18.4	34.8	
First relapse site						
Regional	349 (78.1)	399 (80.3)	0.404	119 (58.1)	105 (73.9)	0.002
Distant	98 (21.9)	98 (19.7)		86 (41.9)	37 (26.1)	
Regional						
Skin	75 (16.8)	138 (27.8)	0.002	38 (18.5)	54 (38.0)	0.001
Lymph node	256 (57.3)	247 (49.7)		78 (38.1)	48 (33.8)	
Skin + lymph node	18 (4)	14 (2.8)		3 (1.5)	3 (2.1)	
Distant						
Skin and/or lymph node	27 (6.0)	27 (5.4)		22 (10.7)	6 (4.2)	
Visceral	47 (10.5)	56 (11.3)		46 (22.4)	22 (15.5)	
Miscellaneous	24 (5.4)	15 (3)		18 (8.8)	9 (6.3)	

AJCC, American Joint Committee on Cancer; ALM, acral lentiginous melanoma; DFI, disease-free interval; DSS, disease-specific survival; LMM, lentigo malignant melanoma; MPM, multiple primary melanoma; NM, nodular melanoma; SAR, survival after recurrence; SSM, superficial spreading melanoma.

[a]Available only after 1999.

Fig. 1



Disease-specific survival (a), disease-free interval (c), survival after recurrence (e) in 1975–1998. Disease-specific survival (b), disease-free interval (d), survival after recurrence (f) in 1999–2011. F, female; M, male.

Table 2. Univariate analyses on (A) DFI, (B) SAR, (C) DSS

	Group A (1975–1998)			Group B (after 1999)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
(A) DFI						
Sex (male vs. female)	1.41	1.24–1.60	<0.001	1.36	1.10–1.69	0.005
Age (years)	1.01	1.01–1.02	<0.001	1.04	1.03–1.05	<0.001
Breslow thickness (mm)						
≤1Br	1			1		
1 < Br ≤ 2	4.73	3.71–6.02	<0.001	6.62	4.36–10.0	<0.001
2 < Br ≤ 4	9.00	7.14–11.3	<0.001	10.8	7.25–15.9	<0.001
Br > 4	15.1	11.9–19.3	<0.001	25.4	17.2–37.4	<0.001
Ulceration (yes vs. no)	3.61	3.12–4.18	<0.001	4.42	3.56–5.48	<0.001
Trunk vs. nontrunk	1.08	0.95–1.23	0.249	0.87	0.71–1.08	0.213
Foot vs. nonfoot	2.08	1.72–2.52	<0.001	1.80	1.24–2.62	0.002
MPM vs. SPM	0.57	0.42–0.76	<0.001	0.67	0.45–0.99	0.044
NM vs. other histotype	2.77	2.39–3.22	<0.001	3.21	2.53–4.08	<0.001
Regression (yes vs. no)				0.45	0.32–0.65	<0.001
(B) SAR						
Sex (male vs. female)	1.66	1.42–1.93	<0.001	1.65	1.22–2.22	<0.001
Age (years)	1.01	1.00–1.01	<0.001	1.03	1.02–1.04	<0.001
Breslow thickness (mm)						
≤1Br	1			1		
1 < Br ≤ 2	4.38	3.24–5.92	<0.001	10.5	5.2–21.0	<0.001
2 < Br ≤ 4	8.39	6.30–11.2	<0.001	18.4	9.41–35.9	<0.001
Br > 4	14.4	10.7–19.2	<0.001	42.7	22.1–82.4	<0.001
Ulceration (yes vs. no)	4.15	3.52–4.89	<0.001	5.05	3.79–6.73	<0.001
Trunk vs. nontrunk	1.29	1.10–1.50	0.001	1.16	0.87–1.55	0.301
Foot vs. nonfoot	1.72	1.37–2.17	<0.001	2.09	1.30–3.37	0.002
MPM vs. SPM	0.38	0.25–0.58	<0.001	0.47	0.25–0.88	0.019
NM vs. other histotype	2.42	2.03–2.88	<0.001	3.13	2.27–4.32	<0.001
Regression (yes vs. no)				0.26	0.14–0.48	<0.001
Site of first metastasis						
In transit	1			1		
Regional lymph node	1.35	1.09–1.67	0.006	1.33	0.89–1.98	0.165
Distant	4.28	3.36–5.44	<0.001	4.30	2.92–6.35	<0.001
(C) DSS						
Sex (male vs. female)	1.67	1.43–1.94	<0.001	1.66	1.24–2.23	<0.001
Age (years)	1.01	1.00–1.02	<0.001	1.03	1.02–1.04	<0.001
Breslow thickness (mm)						
≤1Br	1			1		
1 < Br ≤ 2	4.27	3.16–5.77	<0.001	9.68	4.80–19.5	<0.001
2 < Br ≤ 4	8.39	6.30–11.2	<0.001	17.2	8.78–33.6	<0.001
Br > 4	15.6	11.7–20.9	<0.001	42.8	22.2–82.6	<0.001
Ulceration (yes vs. no)	4.28	3.63–5.04	<0.001	5.25	3.94–7.00	<0.001
Trunk vs. nontrunk	1.26	1.08–1.47	0.004	1.21	0.91–1.61	0.197
Foot vs. nonfoot	1.81	1.44–2.27	<0.001	2.08	1.29–3.34	0.003
MPM vs. SPM	0.35	0.23–0.54	<0.001	0.44	0.23–0.83	0.011
NM vs. other histotype	2.48	2.08–2.95	<0.001	2.95	2.14–4.07	<0.001
Regression (yes vs. no)				0.29	0.16–0.55	<0.001

Br, Breslow thickness; CI, confidence interval; DFI, disease-free interval; DSS, disease-specific survival; HR, hazard ratio; MPM, multiple primary melanoma; NM, nodular melanoma; SAR, survival after recurrence; SPM, single primary melanoma.

Table 3 Multivariate analyses on DFI

	DFI group A (1975–1998)			DFI group B (after 1999)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Sex (male vs. female)	1.24	1.08–1.43	0.002	1.16	0.92–1.46	0.184
Age (years)	1.00	0.99–1.01	0.278	1.02	1.01–1.03	<0.001
Breslow thickness (mm)						
≤1Br	1			1		
1<Br≤2	4.46	3.50–5.68	<0.001	6.02	3.95–9.17	<0.001
2<Br≤4	7.47	5.87–9.51	<0.001	8.27	5.47–12.5	<0.001
Br>4	10.9	8.42–14.3	<0.001	16.5	10.7–25.4	<0.001
Ulceration (yes vs. no)	1.55	1.32–1.81	<0.001	1.39	1.09–1.78	<0.008
Trunk vs. nontrunk	1.31	1.13–1.52	<0.001	1.09	0.86–1.37	0.483
Foot vs. nonfoot	1.71	1.40–2.10	<0.001	1.28	0.87–1.91	0.212
MPM vs. SPM	0.66	0.49–0.88	0.005	0.73	0.49–1.09	0.125
NM vs. other histotype	1.24	1.06–1.46	0.009	1.03	0.79–1.35	0.817

Br, Breslow thickness; CI, confidence interval; DFI, disease-free interval; HR, hazard ratio; MPM, multiple primary melanoma; NM, nodular melanoma; SPM, single primary melanoma.

Table 4 Multivariate analyses on SAR

	SAR group A (1975–1998)			SAR group B (after 1999)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Sex (male vs. female)	1.34	1.13–1.58	0.001	1.24	0.89–1.70	0.196
Age (years)	1.00	0.99–1.01	0.144	1.00	0.99–1.01	0.851
Breslow thickness (mm)						
≤1Br	1			1		
1<Br≤2	1.06	0.78–1.46	0.722	1.61	0.79–3.28	0.193
2<Br≤4	1.19	0.88–1.63	0.250	1.95	0.98–3.89	0.057
Br>4	1.27	0.92–1.77	0.149	2.03	0.98–4.13	0.053
Ulceration (yes vs. no)	1.63	1.35–1.97	<0.001	1.16	0.83–1.61	0.388
Trunk vs. nontrunk	1.21	1.01–1.45	0.042	1.44	1.02–2.02	0.037
Foot vs. nonfoot	1.08	0.83–1.39	0.578	1.41	0.83–2.39	0.197
MPM vs. SPM	0.51	0.33–0.79	0.003	0.57	0.29–1.09	0.088
NM vs. other histotype	0.93	0.76–1.12	0.433	0.72	0.51–1.03	0.077
Site of first metastasis						
In transit	1			1		
Regional lymph node	1.32	1.06–1.64	0.014	1.26	0.84–1.91	0.263
Distant	4.23	3.28–5.46	<0.001	3.74	2.45–5.70	<0.001

Br, Breslow thickness; CI, confidence interval; HR, hazard ratio; MPM, multiple primary melanoma; NM, nodular melanoma; SAR, survival after recurrence; SPM, single primary melanoma.

Table 5 Multivariate analyses on DSS

	DSS group A (1975–1998)			DSS group B (after 1999)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
(A) Nontrunk localization						
Sex (male vs. female)	1.85	1.51–2.26	<0.001	1.70	1.13–2.57	0.011
Age (years)	1.01	1.00–1.02	0.013	1.02	1.00–1.03	0.020
Breslow thickness (mm)						
≤1Br	1			1		
1<Br≤2	3.96	2.64–5.95	<0.001	7.04	2.83–17.5	<0.001
2<Br≤4	6.08	4.07–9.08	<0.001	7.48	3.01–18.6	<0.001
Br>4	9.92	6.45–15.3	<0.001	17.1	6.78–43.1	<0.001
Ulceration (yes vs. no)	2.13	1.69–2.69	<0.001	2.06	1.31–3.24	0.002
Foot vs. nonfoot	1.50	1.17–1.93	0.001	1.63	0.96–2.73	0.067
MPM vs. SPM	0.39	0.21–0.74	0.004	0.69	0.32–1.51	0.357
NM vs. other histotype	0.97	0.77–1.24	0.839	0.60	0.34–1.06	0.081
(B) Trunk localization						
Sex (male vs. female)	0.92	0.71–1.20	0.557	0.93	0.58–1.47	0.751
Age (years)	1.00	0.99–1.01	0.327	1.01	0.99–1.02	0.208
Breslow thickness (mm)						
≤1Br	1			1		
1<Br≤2	4.26	2.71–6.73	<0.001	11.1	3.65–33.9	<0.001
2<Br≤4	8.48	5.46–13.2	<0.001	27.4	9.44–79.7	<0.001
Br>4	11.7	7.31–18.7	<0.001	58.9	20.0–173.3	<0.001
Ulceration (yes vs. no)	1.66	1.23–2.24	0.001	1.17	0.73–1.88	0.508
MPM vs. SPM	0.42	0.23–0.75	0.003	0.33	0.10–0.99	0.050
NM vs. other histotype	1.18	0.87–1.61	0.279	0.93	0.57–1.51	0.775

Br, Breslow thickness; CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; MPM, multiple primary melanoma; NM, nodular melanoma; SPM, single primary melanoma.