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Original Paper

Skin Melanoma in Italy: a Population-based Study on Survival and Prognostic Factors

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Survival and prognostic factors of invasive cutaneous melanoma patients diagnosed in the province of Florence, Italy, were studied using a regression analysis of relative survival rates. The case series consisted of 428 patients reported by the Tuscany Cancer Registry between 1985 and 1989. The effect of gender, age, anatomical site, histological type and microstaging parameters upon relative survival were evaluated using an extension of the Cox proportional hazard model. Five-year relative survival was 70%; 8-year relative survival, referring to a subset of patients, was 67%. In univariate analysis, the following variables were significantly associated with better prognosis: female gender, age younger than 60 years, superficial spreading melanoma (SSM) compared with nodular melanoma (NM), location on the limbs, a thinner lesion according to Breslow, a shallower Clark level. Females had a clear-cut prognostic advantage over males in each category of the variables considered above. After simultaneous adjustment for all other variables, three factors continued to show an independent prognostic effect: age, gender and microstaging parameters (Breslow thickness and Clark level, separately fitted in the model). In the multivariate analysis, the prognostic advantage of females over males was specifically seen for lesions located on the trunk and for both SSM and NM histotype. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE MAJORITY of epidemiological studies on skin melanoma deal with predominantly fair skinned populations [1]. In these, an increase of incidence and mortality has been shown over the last decade [2–4]. However, population-based information about the epidemiology of cutaneous melanoma in the Mediterranean area is less commonly available. Through a descriptive analysis based on the WHO mortality data bank [5], it has been shown that the proportional increase in mortality rates for cutaneous melanoma in southern Europe in the last decade has been larger in comparison with that in the European Community as a whole. However, this result may have been affected by concomitant changes in the quality and completeness of death certification [6].

The incidence rates are lower in the Mediterranean area than those described for a fair skinned population, but the pattern of site predominance by gender and the earlier detection in females are similar [7, 8]. In a recent study on survival of patients diagnosed in 11 Italian population-based cancer registries, the estimated 5-year relative survival in Italy for cutaneous melanoma was 55% for males and 76% for females (1986–1989) [9].

In the present study, a population-based survival analysis, including the variables age, gender, anatomical site, Breslow thickness and Clark level, was performed in an Italian population. Observed and relative survival rates are reported, with the aim of controlling for the competing risk of death. Moreover, the relevance of the available variables as prognostic

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factors was investigated through a proportional hazards regression model.

MATERIALS AND METHODS

Data sources

The Tuscany Cancer Registry (TCR) was the source of the cutaneous melanoma cases. Since 1984, the TCR has collected, registered and analysed information on all malignant tumours in residents of the province of Florence (1 200 000 inhabitants at 1987). The TCR receives copies of patient records from the hospitals in the area, both public and private, from the University hospitals of the region and from the oncological hospitals and services of national importance. Moreover, the pathology departments in the area send information on all tissue specimens with a diagnosis of cancer. The Regional Mortality Registry (RMR) is the source of mortality data utilised by the TCR. Since 1985, the RMR has collected copies of death certificates relative to the residents in the province of Florence. The RMR archives provide cases of cancer not previously reported to TCR and are identified by death certificate only [10]. The detailed procedures of case definition and quality control have been published elsewhere and indicate a good quality and completeness of cancer registration [1].

The TCR registered 432 new cases of invasive cutaneous melanoma (International Classification of Disease, Ninth Revision, code 172) between 1985 and 1989. In the same period, 53 *in situ* cutaneous melanomas were registered (11% of all melanomas). The proportion of cases with histological confirmation was 92.6%. Among these, 41 cutaneous melanomas were diagnosed by histology on lymph node metastases. 33 cases had no histological confirmation.

The age-standardised incidence rate (world as standard) of cutaneous melanoma per 100 000 person-years in the province of Florence between 1985 and 1989 was 4.8 for males and 5.3 for females.

Follow-up

4 of 432 cases were excluded from the survival analysis, because they were identified by death certificate only (0.9%). The index date used for the calculation of survival was the date of incidence of the case (date of first diagnosis of melanoma). The life status of patients at the end of follow-up (31 December 1994) was assessed by record-linkage with the RMR and with the demographic archives of the municipalities of the province. For unlinked cases, the manual registry of the municipality of residence was consulted. Of the 428 cases, 154 had died during the first 5 years of follow-up (176 deaths at the end of 1994). 3 cases were lost to follow-up, because of emigration. These contributed to the person-years calculation only, up to the last date at which they were known to be alive.

Statistical methods

Variables used in describing the survival of cutaneous melanoma patients were: gender; age at diagnosis, classified as < 60 and ≥ 60 years; anatomical site classified as head and neck, trunk, upper limbs, lower limbs and multiple or not specified (NOS); histological type, classified as superficial spreading melanoma (SSM), nodular melanoma (NM), others (acral lentiginous and lentigo maligna) and NOS; diffusion of the disease, defined on the basis of the pathological report derived from surgical samples. This was classified following two criteria: (1) level of invasion according to Clark classification (II to V and not specified) and (2) Breslow thickness categories, in which cut-offs were chosen according to Buttner and colleagues [11]: mm < 1; 1–1.99, 2–3.99, > 3.99, NOS.

The categories 'not specified' for the variables thickness, level of invasion and histological type indicate the 33 cases without histological confirmation and the 41 cases for which the diagnosis was made on the basis of histological examination of lymph node metastases.

The observed survival curves were computed by the actuarial method. End-points were chosen at 1 year intervals up to 8 years after diagnosis, which was the longest available period of follow-up.

Relative survival rates describe survival after controlling for the effect of general mortality. They provide an estimate of patient survival adjusted for the effect of mortality attributable to the competing risk of death, without taking into account the specific causes of death of individual patients. Relative survival rates are calculated as the ratio of observed survival rates versus those expected for subjects in the general population similar to the patients with respect to gender, age and calendar period of observation [12]. The expected survival curve was calculated on the basis of the life tables in the population resident in Florence province.

The effect of gender, age, anatomical site, histological type and stage at diagnosis as prognostic factors for relative survival was evaluated using an extension of the Cox proportional hazard model [13]. This model was fitted to the data using the statistical package GLIM (Generalised Linear Interactive Modelling) [14]. This provides the risk estimate of dying during the follow-up period in a given category of covariates, relative to subjects in the reference category.

RESULTS

The distribution of the 428 cases of invasive cutaneous melanoma by the parameters included in the study is shown in Table 1. No difference by gender was found between the two age classes considered, i.e. < 60 and ≥ 60 years. The predominant histological type in both sexes was SSM followed by NM (more frequent in males than in females). The histopathology category 'others' was more common in females than in males, with twice as many cases of both acral lentiginous melanoma and lentigo maligna (data not shown).

A striking difference between genders is shown by anatomical site and microstaging. Trunk was the most frequent site for males (48%) and lower limbs for females (50%). Head and neck melanomas were more often found in males than in females.

The majority of patients had Clark's level III and IV lesions. Level II lesions were more common in females (19%) than in males (10%). Concerning Breslow thickness, the lesions at the time of diagnosis were thinner in females than in males. The proportion without information for site, histological type and microstaging (level, thickness) was similar in the two genders.

The 1-, 5- and 8-year crude and relative survival rates are shown in Table 2. The 8-year survival refers to a subset of cases ($n = 122$, 40 males, 82 females). After the first year, relative survival was 89%, but it decreased gradually to 70% at the fifth year of follow-up and to 67% 8 years after diagnosis. The 5-year relative survival was 75% for primary cutaneous melanomas, 31% for cutaneous melanomas in which

the diagnosis was made on the basis of histological examination of nodal metastases and 69% for the subset of 33 cases with clinical diagnosis only. Patients in the group aged 60 years or older had a lower survival than younger patients. Upper extremity lesions had the most favourable prognostic outcome, whereas patients with primary lesions of the trunk experienced the poorest survival. NM and the not specified category had the worst prognosis. A significant decreasing trend in survival was observed with increasing thickness categories or increasing Clark level.

Females experienced a clear-cut prognostic advantage over males in each category of the variables considered above (data not shown). Also, for those cases in which the diagnosis was made at the time of nodal metastases, females retained a 5 year better survival (41 versus 24%).

The relative risks (RR) of dying (and their 95% confidence intervals (CI)) during the first 5 years after diagnosis were assessed according to gender, age, anatomical site, histological type and microstaging parameters (Breslow thickness, Clark level) as prognostic variables (Table 3), first in univariate and then in multivariate models. In univariate analysis, female gender, age < 60 years, SSM histotype compared with NM, limbs compared with trunk lesions, thinner lesions according to Breslow categories, a lower Clark level were significantly associated with a better prognosis.

Table 1. *Distribution of incidents of skin melanomas between* 1985 *and* 1989 ⋆ *(and their proportion) in the District of Florence, by prognostic variables and by gender*

	Males $n = 193$ (%)	Females $n = 235$ (%)
Age (years)		
< 60	109 (56)	126 (54)
≥ 60	84 (44)	109 (46)
Site of primary tumour		
Trunk	93 (48)	40 (17)
Head/neck	33 (17)	30 (13)
Upper limbs	23 (12)	36 (15)
Lower limbs	25 (13)	117 (50)
NOS	19 (10)	12 (5)
Histopathology		
SSM	89 (46)	113 (48)
NM	40 (21)	36 (15)
Others	9 (5)	20 (9)
NOS	55 (28)	66 (28)
Clarks level		
II	19 (10)	45 (19)
III	54 (28)	63 (27)
IV	58 (30)	59 (25)
V	12 (6)	9 (4)
NOS	50 (26)	59 (25)
Breslow thickness		
≤ 0.99	25 (13)	59 (25)
1–1.99	37 (19)	42 (18)
2–3.99	38 (20)	36 (15)
≥ 4	31 (16)	20 (9)
NOS	62 (32)	78 (33)
Histological confirmation		
Primary tumour	153 (79)	201 (85)
Metastases	25 (13)	16 (7)
None†	15 (8)	18 (8)

⋆4 of the 432 patients were excluded as they were identified by death certificate only. †Clinical diagnosis only. NOS, not specified; SSM, superficial spreading melanoma; NM, nodular melanoma.

To evaluate the role of each prognostic variable independently from the others, we performed a multivariate analysis including age, gender, anatomical site, histological type and microstaging parameters. Level of invasion and thickness were separately fitted into the model because of their collinearity (Pearson correlation coefficient = 0.77, $P < 0.001$) (Table 3).

After adjustment by all other variables, three factors retained an independent predictive value: age (≥ 60 years: RR = 1.45, 95% CI = 1.11–1.89), gender (females: RR = 0.46, 95% CI = 0.34–0.62), and microstaging defined both by Clark level and Breslow thickness, with a statistically significant trend (Breslow thickness: Wald test = 3.98, $P < 0.001$; Clark level: Wald test = 3.33, $P < 0.001$). In the multivariate models, we also explored a possible interaction term between gender and each other prognostic factor, but no significant effect was identified.

Table 2. *Crude and relative survival rates of patients with skin melanomas diagnosed in the District of Florence between* 1985 *and* 1989

	Years of follow-up					
	Crude survival			Relative survival		
	1	5	8⋆	1	5	8⋆
All	0.87	0.64	0.57	0.89	0.70	0.67
Gender						
Males	0.81	0.52	0.44	0.83	0.58	0.52
Females	0.92	0.74	0.69	0.94	0.81	0.79
Age (years)						
< 60	0.91	0.75	0.70	0.92	0.76	0.73
≥ 60	0.82	0.51	0.42	0.85	0.62	0.59
Anatomical site						
Head/neck	0.87	0.54	0.47	0.91	0.65	0.63
Trunk	0.88	0.58	0.52	0.89	0.63	0.59
Upper limbs	0.92	0.78	0.70	0.93	0.85	0.80
Lower limbs	0.91	0.72	0.66	0.92	0.78	0.76
NOS	0.58	0.48	0.40	0.59	0.53	0.46
Histological type						
SSM	0.97	0.79	0.75	0.98	0.84	0.83
NM	0.87	0.55	0.46	0.89	0.62	0.55
Others	0.93	0.79	0.65	0.96	0.92	0.85
NOS	0.69	0.40	0.33	0.71	0.46	0.41
Clark level						
II	1.00	0.95	0.93	1.00	0.99	0.99
III	0.95	0.79	0.72	0.96	0.84	0.80
IV	0.92	0.58	0.51	0.94	0.64	0.61
V	0.71	0.33	0.24	0.75	0.43	0.35
NOS	0.69	0.41	0.34	0.71	0.47	0.43
Breslow thickness						
≤ 0.99	1.00	0.93	0.89	1.01	0.97	0.95
1.0–1.99	0.97	0.80	0.76	0.98	0.84	0.83
2.0–3.99	0.95	0.66	0.55	0.97	0.75	0.67
≥ 4.0	0.78	0.35	0.30	0.80	0.40	0.38
NOS	0.73	0.47	0.40	0.75	0.54	0.49
Histological confirmation						
Primary CM	0.92	0.68	0.62	0.93	0.75	0.72
Metastases	0.59	0.27	0.17	0.60	0.31	0.22
None†	0.72	0.63	0.59	0.73	0.69	0.67

⋆The 8-year survival refers to a subset of cases ($n = 122$, 40 males, 82 females). †Clinical diagnosis only. NOS, not specified; SSM, superficial spreading melanoma; NM, nodular melanoma; CM, cutaneous melanoma.

Table 3. Relative risk (RR) of dying and 95% confidence intervals (CI) during the first 5 years of follow-up with major prognostic variables (age, gender, anatomical site, histological type, thickness, level of invasion) taken into account separately and adjusted for each other

	Univariate		Multivariate*			
	RR	(95% CI)	Level	(95% CI)	Thickness	(95% CI)
Gender						
Males	1		1		1	
Females	0.36	(0.26–0.49)	0.41	(0.30–0.56)	0.46	(0.34–0.62)
Age (years)						
< 60	1		1		1	
≥ 60	1.83	(1.37–2.44)	1.51	(1.16–1.98)	1.45	(1.11–1.89)
Anatomical site						
Trunk	1		1		1	
Head/neck	1.02	(0.67–1.55)	1.17	(0.79–1.73)	1.25	(0.86–1.84)
Upper limbs	0.31	(0.17–0.59)	0.61	(0.34–1.08)	0.64	(0.37–1.11)
Lower limbs	0.56	(0.38–0.81)	1.21	(0.83–1.76)	1.15	(0.81–1.64)
NOS	1.81	(1.14–2.85)	1.17	(0.74–1.85)	1.15	(0.74–1.80)
Histological type						
SSM	1		1		1	
NM	3.44	(2.28–5.20)	1.76	(0.19–2.62)	1.18	(0.77–1.81)
Others	0.73	(0.21–2.54)	0.53	(0.19–1.47)	0.55	(0.20–1.52)
NOS	6.22	(4.38–8.86)	4.31	(2.52–7.38)	3.20	(1.93–5.30)
Clark level						
II	1		1			
III	7.24	(2.12–24.75)	10.21	(1.81–57.62)		
IV	19.47	(5.90–64.27)	22.74	(4.09–126.37)		
V	38.36	(10.9–134.6)	23.52	(3.97–139.39)		
NOS	38.82	(11.85–127.20)	12.32	(2.11–71.53)		
Breslow thickness						
≤ 0.99	1				1	
1–1.99	4.70	(1.80–12.24)			3.83	(1.58–9.28)
2–3.99	8.00	(3.15–20.30)			5.18	(2.15–12.50)
≥ 4	25.89	(10.60–63.23)			13.74	(5.72–33.01)
NOS	20.37	(8.52–48.71)			5.26	(2.11–13.10)

*Multivariate analysis includes Clark level and Breslow thickness separately. NOS, not specified; SSM, superficial spreading melanoma; NM, nodular melanoma.

In order to quantify further the survival advantage of females, we carried out a multivariate analysis—including thickness as a microstaging parameter—in which males in the first category of each prognostic variable were considered as the reference (Table 4). In this analysis, for each variable the female:male relative risk adjusted for other variables was estimated. After adjustment for other covariates, the female: male risk of dying was lower at a younger age (females:males, approximately 1:3) than at age ≥ 60 years (females:males, approximately 1:2). However, the difference between the two risks was not statistically significant. Concerning site, females retained a statistically significant prognostic advantage over males for lesions located on the trunk (odds ratio (OR) 0.31, 95% CI 0.17–0.57). Also, a better prognosis (an advantage of approximately 70%) was associated with female gender for both SSM and NM.

DISCUSSION

This is, to our knowledge, the first population-based survival study carried out in a Mediterranean population on invasive cutaneous melanoma, which takes into account the main prognostic variables for the disease, such as anatomical site, histological type, Clark level and Breslow thickness. The advantage of studies based on cancer registries over those on hospital series relies on the lack of selection of the cases under study, which are all incident cases in the resident population.

For the 428 cases of invasive cutaneous melanoma collected by the TCR between 1985 and 1989, the overall 5-year relative survival rate for male patients was 58% (62% for primary cutaneous melanoma) and that for females 81%. These survival data are comparable to those obtained in a recent study [9] on survival of cancer patients in Italy (55% in males and 76% in females), but are slightly higher, according to the geographical variability of survival within Italy.

A survival advantage for females was consistently found in our study. In a previous study carried out in the same geographical area, the incidence of thinner lesions (Breslow categories) with favourable prognosis was higher in females than in males (for cases < 0.75 mm, incidence rate in females = 1.4/100 000 versus 0.3/100 000, RR = 0.26, 95% CI 0.1–0.6) [7]. Moreover, females experienced a lower cutaneous melanoma incidence in poorly explorable sites such as trunk [7]. The association between gender and tumour site is well documented, there being a predilection for extremity lesions among women and for trunk lesions among men [8, 11].

The survival advantage for females found in this study was confirmed to be at least partly attributable to differences in anatomical site and probably to a higher awareness about the significance of 'growing moles', resulting in an earlier diagnosis of invasive cutaneous melanoma in females [3].

The multivariate analysis showed a persistent statistically significant lower risk of dying for females after adjustment for all the considered prognostic variables, including anatomical site and thickness of the tumour (multivariate analysis: RR for females = 0.46, 95% CI = 0.34–0.62). It cannot be excluded

Table 4. Relative risk (RR) of dying and 95% confidence intervals (CI) during the first 5 years of follow-up according to major prognostic variables (age, gender, anatomical site, histological type, thickness as microstaging parameter). The risk of death of males in the first category of each variable was considered as the reference category (95% CI)

	Males		Females	
	RR	(95% CI)	RR	(95% CI)
Age (years)				
< 60	1		0.37	(0.25–0.56)
≥ 60	1.26	(0.90–1.76)	0.69	(0.47–1.00)
Anatomical site				
Trunk	1		0.31	(0.17–0.57)
Head/neck	1.04	(0.66–1.66)	0.69	(0.40–1.20)
Upper limbs	0.56	(0.26–1.20)	0.27	(0.12–0.59)
Lower limbs	0.81	(0.47–1.41)	0.56	(0.38–0.82)
NOS	1.28	(0.78–2.09)	0.31	(0.13–0.73)
Histological type				
SSM	1		0.24	(0.13–0.46)
NM	1.07	(0.66–1.74)	0.32	(0.15–0.64)
Others	0.62	(0.18–2.15)	0.13	(0.02–0.71)
NOS	2.13	(1.20–3.78)	1.46	(0.82–2.61)
Breslow thickness				
≤ 0.99	1		0.21	(0.04–1.04)
1–1.99	3.34	(1.11–10.02)	0.65	(0.17–2.50)
2–3.99	3.94	(1.32–11.77)	1.09	(0.29–4.03)
≥ 4.00	9.23	(3.08–27.65)	3.35	(1.03–10.88)
NOS	2.72	(0.87–8.46)	1.82	(0.58–5.67)

NOS, not specified; SSM, superficial spreading melanoma; NM, nodular melanoma.

that residual confounding due to misclassification of microstaging categories may at least partially explain this result. This finding, however, is consistent with that of a larger survival study on 6383 patients, exploring the association with gender of prognostic outcome of caucasian American melanoma patients [15]. No definite reason for female survival advantage is known; it has been hypothesised that the tendency to metastasise is gender-related, as suggested by longer survival in females in the higher Clark level or Breslow thickness category [15], while the difference in prognosis was lost for patients with metastasised melanoma [16]. In the present series, however, in a subset of cases in which the diagnosis was made at the time of nodal metastases, females retained a higher 5-year survival (41 versus 24% in males).

Even within each microstaging category, the gender difference was retained. In the first thickness category (< 0.99 mm), the risk of dying was approximately 4-fold lower for females than for males after adjustment for other prognostic variables, although the difference did not reach statistical significance (RR 0.21, 95% CI 0.04–1.04). Further, it is interesting to note that in multivariate models in which males represented the reference, females experienced a more marked prognostic advantage according to the following conditions: age less than 60 years, lesions involving the trunk and SSM and NM histotype.

The finding of a gender-related prognostic difference within the microstaging and histotype categories is consistent with other studies. In one study, it has been shown that the decline in the estimated 5-year survival rate with increasing thickness differs in the two genders [17]. With 1 mm thickness, survival declined in females by approximately 3% for each 1 mm increase up to 6 mm, declining thereafter by approximately 8% for each additional 1 mm up to 10 mm. For male patients, on the contrary, the survival rate declined—from tumour 1 mm thick thereafter—by about 9% for each 1 mm increment in thickness up to 10 mm. In another study analysing the interaction between prognostic factors of melanoma without nodal involvement, a significant interaction between histotype and Clark level was found in females, but not in males [18]. Specifically, for females with NM, prognosis was essentially independent of Clark level, while in other histotypes, as in males, Clark level represented a strong prognostic factor.

In this series, age had a prognostic effect independent of other variables, as younger patients (< 60 years old) had a lower risk of dying than older patients (> 60 years), both in univariate and multivariate analyses. Some other studies have shown no independent effect of age at diagnosis after adjustment for other prognostic variables such as histological type, site and level of invasion [19, 20]. In contrast, others have shown that age represents an independent prognostic factor [21–23]. Further, the study of the age/gender interaction in a hospital-based series suggested a markedly better prognosis for young women and a poorer prognosis for men and older women after adjustment for relevant variables [24].

The site of primary melanoma, as well as the histological type, was a significant prognostic factor in univariate analysis (better prognosis for limbs compared with head/neck and trunk; better prognosis for SSM compared with NM), but lost significance in multivariate analysis. This result is in agreement with several other studies on melanoma survival [20], but not with others, in which an independent prognostic effect associated with anatomical location was described [22, 25]. Specifically, a poorer prognosis was found for the anatomical location defined as TANS (thorax, upper arms, neck and scalp) in one study [25], and in another for the location on the axis (trunk, head, neck, palms and soles—volar—and under the nails) [22].

As expected in this study, the main prognostic variables were those related to microstaging of melanoma, i.e. Clark level and Breslow thickness, both independent of other covariates, as shown from their separate inclusion in the multivariate model. This finding is in agreement with other studies and it confirms the role of early diagnosis in improving cutaneous melanoma prognosis at a population level.

In conclusion, this study provides a population-based survival analysis of skin melanoma in a southern European population, showing results comparable with those from other western countries. However, the relatively limited proportion of low-stage lesions with their excellent prognosis, strongly suggests the opportunity for early diagnosis practices. The prognostic advantage of females, reported in studies carried out in predominantly fair-skinned populations, was clearly confirmed in this population.

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