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Survival and Prognostic Factors in Patients with Localised Cutaneous Melanoma Observed Between 1980 and 1991 at the Istituto Dermopatico dell'Immacolata in Rome, Italy

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530 patients with localised cutaneous melanoma consecutively observed between 1980 and 1991 at a hospital for skin diseases in Rome, Italy, were studied. Crude survival proportions were calculated with the method of Kaplan and Meier. Cox proportional hazards regression analysis was used to estimate the effect of prognostic factors on death rates. Females and younger patients had better 5- and 10-year survival rates, while increasing tumour thickness was associated with a decrease in survival time. In the multivariate analysis, an independent association with survival was found for tumour thickness, presence of ulceration, age, sex and cross-sectional profile of neoplasia. Our study confirms that females and young patients with thin melanomas have a better prognosis, while the importance of cross-sectional profile needs further study.

Key words: prognostic factors, cutaneous melanoma, survival analysis
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INTRODUCTION

THE SURVIVAL of patients with cutaneous melanoma has generally improved, due to early detection and treatment; however, death rates from this disease have continued to rise, although less rapidly than the incidence rates [1–3], giving support to the concept of a true increase in incidence.

A number of studies have been conducted to investigate the role of several clinical and histopathological features as prognostic factors. It is particularly important to identify the dominant characteristics to be used to accurately predict the prognosis, and classify patients in different risk groups for disease progression. Most studies have indicated tumour thickness and ulceration as the best predictors of prognosis, while a considerable discrepancy exists in the results regarding the association between survival and other histopathological or clinical variables such as sex, age and anatomical site [4–8].

Although tumour thickness has been reported as the single most important prognostic factor [4–10], the behaviour of the cutaneous melanoma in individual cases is difficult to predict. Hence the need to identify other prognostic factors independent from thickness.

This study was undertaken at the Istituto Dermopatico dell'Immacolata (IDI), a large hospital for skin diseases in Rome, Italy, with the aim of determining the prognostic importance of certain histopathological and clinical variables for patients with localised cutaneous melanoma.

PATIENTS AND METHODS

Patients

Between 1 January 1980 and 31 December 1991, 530 cases of cutaneous melanoma were identified from the records of patients

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attending the Outpatient Plastic Surgery Department and inpatients admitted to the hospital to undergo melanoma excision. The slides of all patients were reviewed by the IDI pathologist at the outset of the study. The characteristics of the tumours recorded were cross-sectional profile, histological type, level of dermal invasion, tumour thickness, predominant cell type, mitotic rate, evidence of regression and presence of ulceration.

The mitotic rate was defined as low, medium or high. The number of mitoses counted per five high power fields was less than 1, 1 to 5 or more than 5, respectively.

Ascertainment of outcome

The status of the patients as of 30 June 1992 was determined from the local census offices and the local death registers were searched for the causes of death. For patients whose cause of death was not recorded in the local registers, the records of death for specific causes of the Italian Central Statistical Office was consulted.

The patients who died from causes other than melanoma were considered to be censored at the time of death.

Statistical analysis

Crude survival proportions were calculated by the method of Kaplan and Meier [11]. Differences in survival distributions were tested with the log-rank test.

The prognostic role of several clinical and histopathological variables was investigated by the Cox proportional hazards regression model [12], defined by:

$$h_j(t)/h_0(t) = e^{\beta_1 x_{1j} + \beta_2 x_{2j} + \beta_3 x_3 + \cdots}$$

where $h_j(t)$ is the hazard function for a specific individual, and $h_0(t)$ is the baseline hazard function for the study population. The ratio $h_j(t)/h_0(t)$ can be considered to be constant and its value depends on the characteristics of the individual, expressed by the explanatory variables x_{1j}, x_{2j} ...

Cox suggested that the fixed ratio of the two hazard functions be considered as an exponential function of the explanatory variables. The value of β is the natural logarithm of the relative risk of death:

$$\text{In relative risk} = \beta_1 x_{1j} + \beta_2 x_{2j} + \beta_3 x_{3j} + \ldots$$

The β coefficients can be interpreted more correctly as fatality rate ratios. In other words, they estimate, for a given category of a variable, the risk of moving from the reference category to that category. The goodness of fit was checked graphically according to Andersen [13]. The BMDP Statistical Software, version 1990, was used for statistical calculations.

RESULTS

Among the 530 patients identified, 12 had evidence of lymph node metastatic involvement at the time of the diagnosis and were excluded from the analysis. Of the 518 patients with localised cutaneous melanoma identified between 1980 and 1991, only 83 (16.0%) were lost to follow-up after the first observation. The clinical and histopathological characteristics of the subjects lost to follow-up, as compared with the subjects with complete follow-up, are listed in Table 1. Among the subjects lost to follow-up, there was a statistically significant higher proportion of subjects with head/neck lesions, with lesions ≤0.75 mm thick, and with lentigo maligna melanomas.

There were 95 deaths, 89 due to melanoma. The median follow-up time was 52 months (range 4–149, mean 57).

Table 1. Characteristics of the study population and comparison with the subjects lost to follow-up

	Subjects with complete follow-up		Subjects lost to follow-up	
	n	%	*n*	%
Sex				
Male	192	44.1	30	36.1
Female	243	55.9	53	63.9
Age (years)				
15–49	189	43.4	39	47.0
50–59	93	21.4	13	15.7
60–69	74	17.0	17	20.5
≥70	79	18.2	14	16.9
Anatomical site				
Head/neck	67	15.4	21	25.3*
Trunk	174	40.0	29	34.9
Upper limb	57	13.1	5	6.0
Lower limb	136	31.3	27	32.5
Other	1	0.2	1	1.2
Breslow thickness (mm)				
0.00–0.75	127	29.2	39	47.0†
0.76–1.49	100	23.0	13	15.7
1.50–3.00	123	28.3	27	32.5
>3.00	85	19.5	4	4.8†
Level of invasion (Clark)				
I	58	13.3	27	32.5†
II	78	17.9	14	16.9
III	49	11.3	12	14.5
IV	236	54.3	29	34.9†
V	14	3.2	1	1.2
Histological type				
Superficial spreading	295	67.8	48	57.8
Nodular	79	18.2	16	19.3
Acral lentiginous	21	4.8	3	3.6
Lentigo maligna	40	9.2	16	19.3†
Cross-sectional profile				
Flat	224	51.5	52	62.7
Convex or plateau-like	166	38.2	25	30.1
Nodular–polyploid	45	10.3	6	7.2
Cell type				
Epithelioid	89	20.5	13	15.7
Spindle	56	12.9	12	14.5
Clear	3	0.7	0	—
Naevocytic	207	47.6	40	48.2
Mixed	80	18.4	18	21.7
Mitotic rate				
Low	243	55.9	52	62.7
Medium	101	23.2	16	19.3
High	91	20.9	15	18.1
Regression				
Present	106	24.4	18	21.7
Absent	329	75.6	65	78.3
Ulceration				
Present	137	31.5	14	16.9†
Absent	298	68.5	69	83.1

*$P<0.05$, †$P<0.01$.

Survival analysis

The 5- and 10-year survival proportions in relation to clinical and histological characteristics are listed in Table 2. In our study, women had a better 10-year survival than men (75.6 versus 62.2%, $P<0.001$). Increasing age was significantly associated with a decrease in survival rate (P for trend <0.001). No difference was found in survival rates for different anatomical locations, although the analysis of subsites in the head/neck

Table 2. Five- and ten-year survival rates by clinical and histopathological features

	n	%	5-year % survival	10-year % survival	χ^{2*}	*P* value†
Study patients	435					
Sex						
Male	192	44.1	71.9	62.2		
Female	243	55.9	86.7	75.6	13.63	0.0002
Age (years)						
15–49	189	43.4	87.2	75.0		
50–59	93	21.4	85.5	77.4		
60–69	74	17.0	73.8	62.6		
≥ 70	79	18.2	61.3	49.0	15.31	0.0001‡
Anatomical site						
Head/neck	67	15.4	85.5	66.4		
Trunk	174	40.0	77.3	69.6		
Upper limb	57	13.1	82.4	76.4	0.74	0.3905§
Lower limb	136	31.3	80.4	68.1	0.05	0.8216§
Other	1	0.2	100.0	—	0.158	0.6912§
Breslow thickness (mm)						
0.00–0.75	127	29.2	97.9	97.9		
0.76–1.49	100	23.0	92.7	85.1		
1.50–3.00	123	28.3	72.3	48.9		
>3.00	85	19.5	51.5	40.6	84.17	0.0000‡
Level of invasion (Clark)						
I	58	13.3	100.0	100.0		
II	78	17.9	96.7	96.7		
III	49	11.3	93.1	82.7		
IV	236	54.3	71.8	57.4		
V	14	3.2	21.4	—	62.71	0.0000‡
Histological type						
Superficial spreading	295	67.8	82.9	73.0		
Nodular	79	18.2	62.8	46.4	21.6	0.0000‖
Acral lentiginous	21	4.8	85.2	85.2	0.28	0.5984‖
Lentigo maligna	40	9.2	94.1	94.1	4.32	0.0376‖
Cross-sectional profile						
Flat	224	51.5	94.1	91.9		
Convex or plateau-type	166	38.2	67.5	49.7	54.94	0.0000¶
Nodular-polyploid	45	10.3	62.4	44.8	52.47	0.0000¶
Cell type						
Epithelioid	89	20.5	79.9	65.2	3.17	0.0751**
Spindle	56	12.9	73.1	59.5	3.85	0.0497**
Clear	3	0.7	100.0	—	0.40	0.5255**
Naevocytic	207	47.6	85.9	80.5		
Mixed	80	18.4	70.8	61.0	11.77	0.0006**
Mitotic rate						
Low	243	55.9	91.6	79.8		
Medium	101	23.2	71.1	65.4		
High	91	20.9	60.1	48.8	49.07	0.0000‡
Regression						
Present	106	24.4	92.6	87.0		
Absent	329	75.6	76.2	64.1	12.47	0.0004
Ulceration						
Present	137	31.5	56.6	45.5		
Absent	298	68.5	90.9	80.6	68.92	0.0000

*Degrees of freedom = no. of groups compared less 1. †Log-rank test. ‡Test for trend (Mantel-Cox). §Reference category: head/neck. ‖Reference category: superficial spreading. ¶Reference category: flat. **Reference category: naevocytic.

group revealed some differences, with scalp/neck lesions having a worse 5-year survival than face lesions (37.5 versus 88.0%). This difference was not statistically significant, there being only 4 cases in the scalp/neck group. The increase of tumour thickness was inversely related to the survival rates; the same association was found with increasing level of invasion (*P* for trend <0.001). Patients with nodular melanoma had the worst survival rate, while patients with lentigo maligna melanoma had the best. The presence of ulceration reduced the probability of survival; conversely, the presence of regression seemed to be associated with better survival rates. The mitotic rate was positively associated with survival.

No difference in overall survival proportions was found when patients were grouped according to the year of treatment.

Multivariate analysis

The 58 patients with Clark level I were excluded from this analysis. The final model was built in a stepwise fashion after testing each explanatory variable in an univariate analysis. The strongest effect on survival was seen when age (years) was categorised in three levels: 15–49, 50–59, 60+. Breslow thickness and Clark level were strongly correlated to each other (r=0.72, P<0.001), although some variation in thickness was present in each level. For example, in our dataset, in Clark level IV melanomas all the thickness categories were represented: 22% of level IV melanomas were ≤ 1.49 mm thick, 47% were 1.50–3.00 mm, and 31% were > 3 mm. The survival rates among the subjects with level IV varied according to Breslow thickness (Figure 1). On the basis of these findings, tumour thickness and level of invasion were not included simultaneously in the model. The final model included Breslow thickness, age, sex, presence of ulceration, cross-sectional profile, mitotic rate, presence of regression, and histological type. The rate ratios and 95% confidence intervals estimated by the Cox model are shown in Table 3.

Tumour thickness was the strongest predictor of outcome. The cross-sectional profile of the melanoma and the presence of ulceration were the only other histopathological factors that independently affected the fatality rates. After adjusting for the other pathological characteristics, the mitotic rate and the presence of regression did not affect the prognosis. Age and sex still had a relevant influence on prognosis after the other covariates included in the model were accounted for. No independent effect was found for mitotic rate, histological type or presence of regression.

DISCUSSION

Tumour thickness, as reported by many authors [6,7,9,14], was found to be the most important indicator of prognosis both in the univariate and multivariate analyses. Level of invasion as a single factor was significantly associated with survival, but it was not included in the multivariate analysis since it is highly correlated with thickness, and this poses problems of multicolinearity. In addition, as recognised by other authors [8,15], there is heterogeneity of tumour thickness in the different levels of invasion, and survival rates in each level are influenced by thickness. The reverse relationship is not observed consistently. Furthermore, Breslow thickness as a quantitative variable has been indicated as the histopathological characteristic less subject to interobserver variation [16] and, consequently, it seems a more accurate prognostic factor than level of invasion. More recently, the growth phase of melanomas, including thin melanomas, has been indicated as the most accurate predictor of survival [10], but its role as a prognostic factor deserves further study.

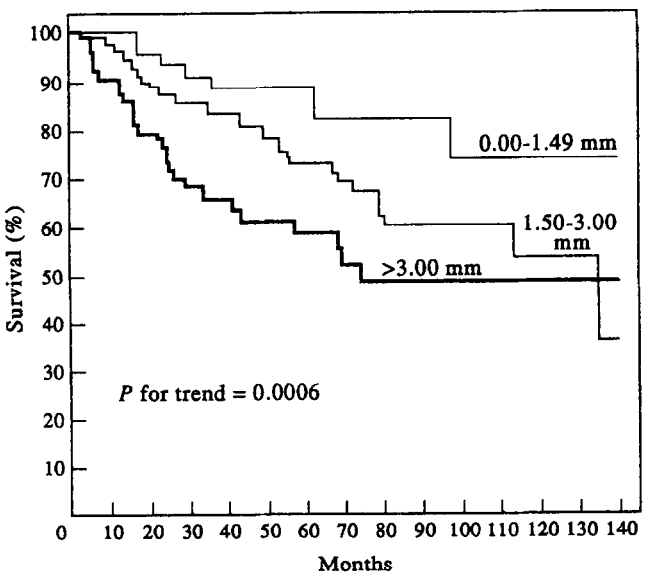

Fig. 1. Survival rates for patients with Clark level IV melanoma by thickness categories

The role of anatomical location as a prognostic factor was not observed in our study. The importance of anatomical site as an independent predictor of survival is still controversial, as the association of survival with the tumour location has been inconsistently reported by other studies. Differences in grouping of anatomical sites add further difficulty to the comparison of results from different studies. Some authors reported a significant association between survival and scalp/neck locations [6,17]. The difference in survival between patients with scalp/neck lesions versus patients with face lesions noted in our study needs further evaluation with a larger number of cases.

The prognostic importance of ulceration, reported by many studies [4,5,7,8,18] was confirmed in our data.

Surprisingly, the cross-sectional profile of neoplasia had an effect on prognosis even after adjusting for tumour thickness, since subjects with convex/plateau-like or nodular/polypoid lesions had a poorer prognosis than patients with flat lesions. An explanation for this finding could be a tendency for these tumours to be more rapidly invasive.

In our data, age and sex were found to be independent prognostic factors. The survival advantage of female patients has been observed in several studies [8–10, 18]. A number of possible explanations have been proposed: in a large study [8], women were found to have thinner and less ulcerated melanomas than men, and lesions located more frequently on the lower extremities, a site considered more favourable. In our data, no statistically significant difference was observed in Breslow thickness between males and females, although there was a tendency for females to have thinner lesions. In contrast, a significantly higher proportion of males than females had an ulcerated melanoma (44.1 versus 30.1%, P <0.01).

Mitotic rate, although inversely associated with survival in univariate analysis, had no independent prognostic value when other factors were accounted for. However, the number of mitoses per square millimeter has been indicated as a strong prognostic factor in other studies [5,10], and has been used in the construction of a prognostic index, it appearing to be a more accurate predictor of survival than thickness alone [19,20].

The role of regression is still controversial. In our study, histological evidence of regression, after adjusting for other prognostic factors, had no effect on survival. Regression has been associated with a poor survival only in tumours in the vertical growth phase [10], and has been reported as a factor negatively influencing the prognosis of thin melanomas [21]. Other authors have not observed an influence of regression on survival [21,22]. A major reason for such a discrepancy lies in the absence of a univocal histological definition of regression.

We did not find the histological type of melanoma to be an independent indicator of prognosis. In fact, the tendency noted

Table 3. Fatality rate ratios and 95% confidence intervals for patients with invasive melanoma (n=377). *Final Cox regression model*

	Deaths	Total	Rate ratio	95% confidence interval	Wald Test χ^{2*}	*P* value
Breslow thickness (mm)						
0.00–0.75	2	69	1.00			
0.76–1.49	10	100	2.44	0.51–11.71	1.25	0.2632
1.50–3.00	38	123	4.48	0.94–21.47	3.53	0.0603
≥3.00	39	85	8.35	1.69–41.26	6.77	0.0093
Ulceration						
Absent	31	241	1.00			
Present	58	136	1.68	1.01–2.79	4.05	0.0442
Sex						
Female	34	216	1.00			
Male	55	161	2.22	1.44–3.44	12.83	0.0003
Age (years)						
15–49	31	170	1.00			
50–59	13	77	1.25	0.64–2.42	0.42	0.5147
≥60	45	130	2.28	1.38–3.77	10.30	0.0013
Cross-sectional profile						
Flat	12	166	1.00			
Convex or plateau-like	58	166	2.16	1.00–4.65	3.87	0.0491
Nodular-polypoid	19	45	1.91	0.76–4.79	1.89	0.1697
Mitotic rate						
Low	27	191	1.00			
Medium	25	95	1.20	0.67–2.12	0.37	0.5423
High	37	91	1.23	0.70–2.18	0.52	0.4710
Regression						
Absent	80	295	1.00			
Present	9	82	0.67	0.31–1.42	1.14	0.2865
Histological type						
Superficial spreading	53	270	1.00			
Nodular	33	79	0.63	0.37–1.10	2.63	0.1048
Acral lentiginous	2	18	0.64	0.15–2.73	0.36	0.5470
Lentigo maligna	1	10	0.79	0.10–6.61	0.05	0.8307

*Degrees of freedom = 1.

in the univariate analysis for nodular melanomas to have a poorer survival rate disappeared when tumour thickness and ulceration were accounted for.

Finally, 16% of patients were lost to follow-up after the first observation, but since it is unlikely that prognostic variables other than those evaluated in this study have had a selective role, we consider they exerted a negligible effect on our findings.

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Phase II Trial of 5-Fluorouracil and the Natural *l* Isomer of Folinic Acid in the Treatment of Advanced Colorectal Carcinoma

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Between February 1991 and July 1992, 79 previously untreated patients with metastatic colorectal carcinoma were enrolled in a phase II study of combined 5-fluorouracil (5-FU) and *l*-folinic acid (FA). 5-FU 370 mg/m²/day was administered for 5 consecutive days as an intravenous (i.v.) bolus injection preceded by *l*-FA 100 mg/m²/day with the same administration modality. Treatment was given every 4 weeks until progression. 79 patients were evaluable for toxicity and 64 for response. 2 patients (3%) achieved a complete remission and 8 (12.5%) a partial remission, 33 (52%) had stable disease and 21 patients (33%) had progressive disease. Median duration of remission was 32.5 weeks and median survival for all evaluable patients was 64.5 weeks. Substantial to severe side-effects occurred in 39% of patients. Dose-limiting toxicity (grade 3–4) was mainly diarrhoea (18%) and mucositis (15%). Nausea/vomiting, cutaneous toxicity, leucopenia, alopecia and conjunctivitis of grade 3–4 occurred respectively in 6, 4, 2.5, 1 and 1% of cases. Toxicity appeared to be substantially similar to that characteristic of combined 5-FU and the chiral mixture of *d,l*-FA. Efficacy was within the range of that observed with the 5-FU/*d,l*-FA combination, although at the lower level.
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INTRODUCTION

RELEVANT CLINICAL results have recently been obtained in the treatment of patients with advanced gastrointestinal carcinomas by selectively potentiating the antitumour activity of 5-fluorouracil (5-FU) with modulating drugs (e.g. methotrexate, phosphonacetyl-L-aspartic acid, folinic acid) which interfere with its metabolic pathways [1].

In particular, the ability of folinic acid (FA) to enhance the clinical efficacy of 5-FU has been demonstrated in patients with colorectal adenocarcinoma; the objective response rate after treatment with 5-FU and FA has been reported to be as high as 13% in patients previously exposed to 5-FU alone and 30% in previously untreated patients [1, 2]. The majority of comparative trials have also demonstrated a significant advantage of the combination of 5-FU and FA over 5-FU alone in terms of objective response [3–10], and some studies have also shown increased survival [4, 5]. However, a minority of these studies contradict the general trend, not showing significant differences in response [11, 12]. A meta-analysis, including all published phase III studies, suggests that 5-FU and FA may offer a definite advantage over 5-FU alone in the treatment of advanced colorectal cancer [13].

In several human tumour cell lines [1, 2] and in tumour explants from patients [14–16], the extent and duration of the inhibition of thymidylate synthase by fluorodeoxyuridylate, the main active metabolite of 5-FU, constitute important determinants of sensitivity to the fluoropyrimidine.

Preclinical and clinical studies have shown that increased concentrations of the cofactor 5,10-methylenetetrahydrofolate, which are generated after administration of FA, enhance forma-