Virchows Arch [Pathol Anat] (1985) 406:179–195

Virchows Archiv A
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Survival with primary cutaneous malignant melanoma, evaluated from 2012 cases

A multivariate regression analysis

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Summary. Cox's multivariate regression model for survival data was applied to 2,012 patients with primary cutaneous melanoma in order to evaluate the relative prognostic value of numerous clinical and histological variables and to establish their prognostically most efficient combination. The material was divided into 4 groups according to the size of resection margin of the primary lesion (<2.0 cm, 2.0 cm, 2.1–4.9 cm, and $\geqq 5.0$ cm). Data were analysed separately in these 4 groups and equivalent results were obtained.

The risk factors were clinical stage, site of tumour, tumour thickness, level of invasion, mitotic activity, ulceration, lymphocytic reaction, predominant type of invasive tumour cell and partial regression. When accounting for these factors, histological type, nuclear pleomorphism, nucleolar size, vascular invasion, pigmentation, verrucous growth pattern, and dermal elastosis were without prognostic influence. The effect of sex and age of patient was uncertain and both variables, therefore, were retained in the model. By using Cox's method it is possible to make a qualified estimate of the survival for the individual patient.

Key words: Malignant melanoma – Cutaneous – Prognosis – Multivariate regression analysis

Introduction

The clinical course of cutaneous malignant melanoma after treatment is extremely variable and depends on the clinical as well as the histological features of the primary tumour (Petersen et al. 1962, Cochran 1969, Clark et al. 1969, McGovern 1970, McGovern et al. 1973, Søndergaard and Hou-Jensen 1977, Schmoeckel and Braun-Falco 1978, McGovern et al. 1979,

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Table1. Levels of invasion employed in the present study

Level I	All tumour cells were above the epidermal basement membrane.
Level II a	Tumour was confined to the papillary dermis without reaching the *papillary-reticular interface (PRI).*
Level II b	One or few isolated tumour nests of PRI
Level III a	In a single area of the melanoma the tumour cells filled out the papillary dermis and impinged upon PRI.
Level III b	In the major invasive part of the melanoma the tumour cells filled out the papillary dermis and impinged upon upon PRI.
Level IV a	Unequivocal tumour infiltration of the superficial layer of the reticular dermis by less than 50 tumour cells per cross section.
Level IV b	More than 50 tumour cells infiltrating $\leqq 0.15$ mm into the reticular dermis.
Level IV c	More than 50 tumour cells infiltrating > 0.15 mm into the upper half of the reticular dermis.
Level IV d	Tumour cells infiltrating the lower half of the reticular dermis.
Level IV e	Tumour reaching the reticular-subcutaneous interface.
Level V a	Tumour infiltrating the subcutaneous tissue.
Level V b	Tumour extending into the subcutaneous tissue surrounded by a fibrotic rim.
Level PM II	Polypoidal melanoma in which the tumour cells did not reach PRI.

Søndergaard and Olsen 1980, Drzewiecki et al. 1980). Cox's multivariate regression analysis (1972) permits the study of many variables simultaneously. In order to evaluate the relative prognostic value of clinical and histological characteristics of cutaneous melanoma the fate of 2,012 melanoma patients was examined by Cox's regression analysis. The study was based on unselected material from a geographically well defined part of Denmark. One important result of the identification of the prognostically significant characteristics of malignant melanoma and their relative influence on survival is that a qualified estimate of survival may be calculated for each patient, as illustrated by an example.

Material and methods

During the period January 1949 to April 1978 2,469 patients were treated for cutaneous melanoma and followed up clinically at the Finsen Institute in Copenhagen. In 2,012 of the patients the histological material from the primary cutaneous melanoma was available and suitable for microscopic reclassification, which was done by one person (KS). Histologically all the 2,012 lesions were primary cutaneous melanomas with dermal invasion. 343 of the 2,012 patients were included in the study by Olsen (1966).

All primary melanomas were treated by complete surgical excision as described by Olsen (1966). After surgery the patients were followed up clinically at regular intervals for at least 10 years.

For the purpose of this investigation the patients were studied until October 1980 and withdrawn when they had been followed up clinically for 10 years. If a patient was followed

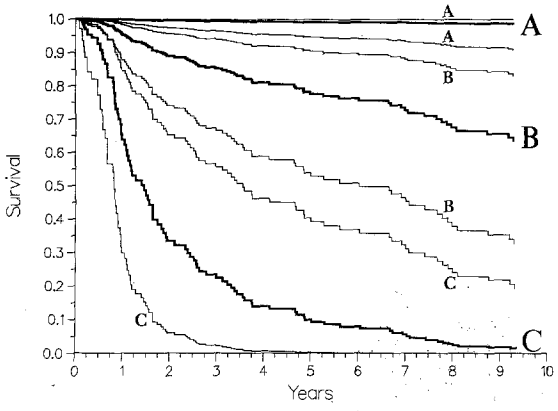

Fig. 1. Survivorship functions for a patient with low (**A**), medium (**B**), and high risk (**C**) treated by resection margin <2.0 cm. By A, B, and C are indicated the 95% confidence limits for the survivorship functions **A, B,** and **C**

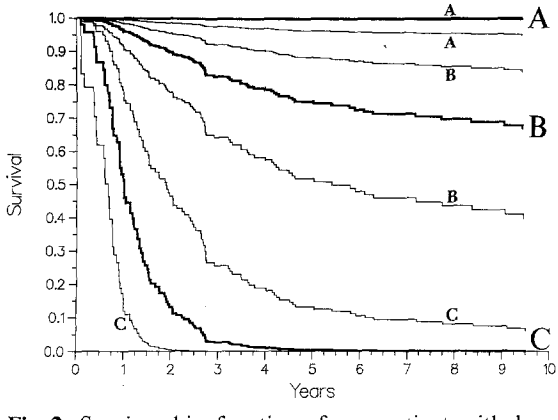

Fig. 2. Survivorship functions for a patient with low (**A**), medium (**B**), and high risk (**C**) treated by resection margin 2.0 cm. By A, B, and C are indicated the 95% confidence limits for the survivorship functions **A, B,** and **C**

up for less than 10 years information was collected from the National Registration Offices concerning the patient's possible death. In case of death, the cause was established by information from the patient's case record from the Finsen Institute, the hospital in which the patient died, and the death certificate.

The recording of the clinical and histological characteristics were made separately.

The clinical information included:

- sex and date of birth of patient,
- clinical stage at the time of surgery in accordance with Olsen (1966),
- date of surgery,
- minimum distance from the edge of tumour to the margin of the final excision,
- date and state of exit from the study,
- site of tumour.

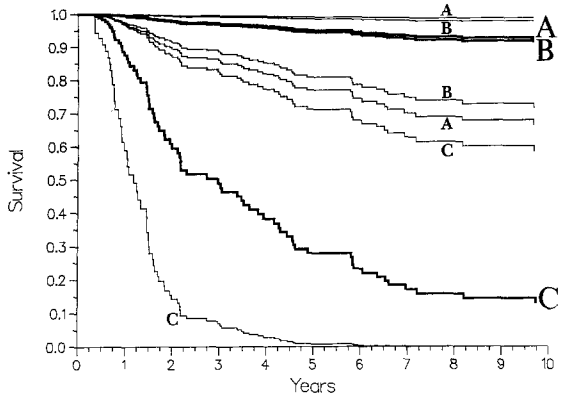

Fig. 3. Survivorship functions for a patient with low (**A**), medium (**B**), and high risk (**C**) treated by resection margin 2.1–4.9 cm. By A, B, and C are indicated the 95% confidence limits for the survivorship functions **A, B,** and **C**

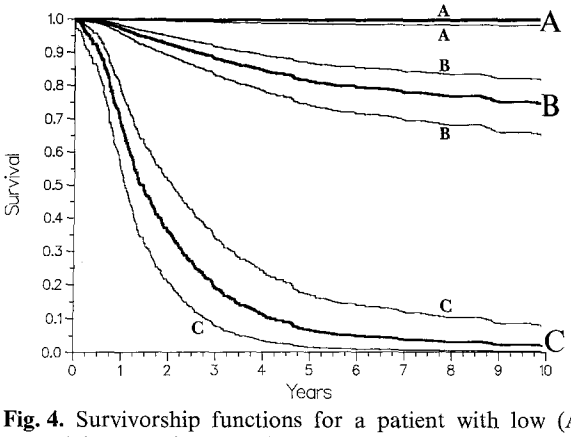

Fig. 4. Survivorship functions for a patient with low (**A**), medium (**B**), and high risk (**C**) treated by resection margin ≥ 5.0 cm. By A, B, and C are indicated the 95% confidence limits for the survivorship functions **A, B,** and **C**

The histological classification included the following characteristics:

Histological type of melanoma was classified in accordance with Clark et al. (1969) and McGovern et al. (1973) as previously described (Søndergaard 1983A): lentigo maligna melanoma (*LMM*), superficial spreading melanoma (*SSM*), nodular melanoma (*NM*), and unclassifiable melanoma.

Depth of invasion was staged by a modification of the staging system proposed by Clark et al. (1969), see Table 1. No melanomas level I were included in the present material.

Tumour thickness was measured in mm to 2 decimal places from the top of the epidermal granular cell layer to the deepest point of invasion (Breslow 1970 and 1975), as previously described (Søndergaard 1980).

The number of mitoses was counted in 10 consecutive microscopic high power fields ($=0.96\ mm^2$) in the area of greatest mitotic activity, and was expressed as mitoses/mm^2. In very small lesions where 10 h.p.f. could not be examined the number of mitoses was not counted.

Ulceration, if present, was measured by an ocular micrometer on one cross-section. If more ulcerations were found in the same cross-section their extensions in mm were added. A crusta without ulceration was also recorded.

Pigmentation of the invasive tumour cells was expressed as average pigmentation by a 0–4 scale corresponding with no, slight, moderate, marked and extraordinarily pronounced pigmentation.

The dominant invasive cell type was recorded as nevoid, epithelioid, spindle, balloon, or an equal mixture of 2 or more cell types.

Lymphocytic reaction beneath the deep aspect of the invasive part of the tumour was expressed by a 0–4 scale modified from the system of Lund et al. (1977). 4 corresponded to a continuous band of lymphocytes beneath the invasive part of tumour, 3 to a discontinuous band leaving 1 or 2 islands of tumour cells without inferior lymphocytic accumulation measuring <0.5 mm each, 2 to many large patches of lymphocytes, 1 to a few small patches of lymphocytes, and 0 to no lymphocytic reaction.

Nuclear pleomorphism was expressed by a 1–4 scale with 1 for lowest and 4 for highest pleomorphism.

Nucleolar size was indicated as the diameter of the nucleoli in those regions of tumour where the greatest nucleoli could be found. H.p.f. and ocular micrometer with 2.5 μm units were used.

Partial regression of melanoma was defined as fibrotic areas with no or few tumour cells and variable amounts of melanophages and lymphocytes. No completely regressed melanomas were included.

Solar elastosis of the dermis was staged from 0 to 3 as no, slight, moderate, and marked elastosis.

Vascular invasion was recorded only when unequivocal.

Verrucous growth pattern of the melanoma was recorded if present.

The distribution of the patients on the categories of the clinical and histological variables is given in Table 2.

Statistical methods

As the objective of the study was to evaluate survival from malignant melanoma in relation to various clinical and histological characteristics, the response variable was time from radical surgery until death from malignant melanoma. Observation times for patients leaving the study for reasons other than death from malignant melanoma were considered as censored observations.

The statistical model chosen was the semiparametric regression model introduced by Cox (1972) in which the death rate (hazard rate), $\lambda(t; z_i)$, for the i'th patient at time t after surgery is given as an underlying (common) death rate $\lambda_0(t)$ multiplied by an exponential function of the covariate vector z_i specific for the i'th patient thus yielding a model of proportional hazard rates:

$$\lambda(t; z_i) = \lambda_0(t) \exp\{\beta_1 z_{i1} + \ldots + \beta_p z_{ip}\}.$$

Here $\lambda_0(t)$ is the unknown and unspecified death rate for a (possible fictive) patient for whom the covariate vector z_i equals zero, and $\beta_1, \ldots, \beta_p$ are the unknown parameters to be estimated.

The scoring of the covariates is of great importance for the validity of the model. A series of graphical goodness-of-fit tests was performed in order to find an appropriate scoring of the covariates, as described by Andersen (1982). Estimation of the parameters was performed

Table 2. Initial grouping of the clinical and histological variables and the distribution of 2,012 patients. (The number of unclassifiable cases is not shown)

No.	Variable	Grouping	No. of patients
1	Sex	Male	723
		Female	1,289
2.	Age at final excision	<20	20
		20–29	142
		30–39	306
		40–49	438
		50–59	427
		60–69	373
		70–79	242
		80–	64
3.	Clinical stage	I	1,767
		II	200
		III	45
4.	Size of resection margin	<2 cm	276
		2 cm	318
		2.1–4.9 cm	179
		≧5 cm	1,239
5.	Site of tumour	Hand and foot	173
		Thigh (knee included)	161
		Lower leg	438
		Head (excluding ears)	283
		Ear	33
		Neck	52
		Trunk	629
		Lower arm	79
		Upper arm	151
		Genitals and perianal region	13
6.	Histological type	NM	531
		LMM	85
		SSM	1,299
7.	Levels of invasion	IIa	289
		IIb	54
		IIIa	164
		IIIb	519
		IVa	77
		IVb	57
		IVc	382
		IVd	172
		IVe	34
		Va	138
		Vb	42
		PM II	67
8.	Tumour thickness	–0.49 mm	199
		0.50–0.99 mm	308
		1.00–1.49 mm	244
		1.50–1.99 mm	194
		2.00–2.49 mm	202
		2.50–2.99 mm	142

Table 2 (continued)

No.	Variable	Grouping	No. of patients
		3.00–3.49 mm	147
		3.50–3.99 mm	106
		4.00–4.49 mm	70
		4.50–4.99 mm	66
		5.00–5.49 mm	51
		5.50–5.99 mm	49
		6.00– mm	223
9.	Number of mitoses per mm^2	0	119
		1–4	631
		5–9	439
		10–14	220
		15–19	142
		20–24	91
		25–29	28
		30–34	20
		35–	24
		<1 mm^2 tumour tissue	261
10.	Ulceration	0 mm	1,250
		1– 4 mm	271
		5– 9 mm	183
		10–14 mm	94
		15–19 mm	50
		20–24 mm	21
		25– mm	27
		Crusta	101
11.	Pigmentation	0	431
		1	440
		2	530
		3	524
		4	86
12.	Dominant cell type	Nevoid	130
		Epithelioid	1,207
		Spindle	150
		Balloon	0
		Mixture	523
13.	Lymphocytic reaction	0	346
		1	797
		2	338
		3	219
		4	297
14.	Nuclear pleomorphism	1	182
		2	711
		3	818
		4	227
15.	Nucleolar size	<2.5 μm	323
		2.5 μm	772
		2.5–3.7 μm	464
		3.7 μm	226
		3.7–5.0 μm	118
		>5.0 μm	29

Table 2 (continued)

No.	Variable	Grouping	No. of patients
16.	Solar elastosis	0	1,722
		1	56
		2	147
		3	79
17.	Vascular invasion	No	1,908
		Yes	104
18.	Verrucous growth pattern	No	1,953
		Yes	59
19.	Deep tumour invasion along skin appendages	No	1,859
		Yes	153
20.	Partial regression	No	1,731
		Yes	281

by maximizing Cox's (1972) likelihood function and an estimate $\hat{A}_0(t)$ of the cumulative underlying death rate $A_0(t)$ was obtained by the method of Breslow (1982). The computations were performed by a modified version of the computer programme FCN (Kalbfleisch and Prentice 1980). Tests of hypotheses about the β's were performed as likelihood ratio tests assuming the approximate chi-squared distribution.

Due to the large number of covariates to be considered, a modified backward elimination procedure was adopted. The covariates were grouped as to their *a priori* assumed prognostic importance, and only the most important variables were included in the first phases of the analysis. As the eliminating procedure progressed, space was left for inclusion of less important variables and so on.

Results

Initially, the variables were scored according to the very detailed grouping given in Table 2. The sizes of the resection margin fell naturally into 4 groups, <2.0, 2.0, 2.1–4.9, and $\geqq 5.0$ cm, and in order to obtain the most precise evaluation of the effect of the non-therapeutic variables, the data were analysed separately by Cox's method in these 4 groups. Equivalent results were obtained in the four groups.

The model building and goodness-of-fit test procedures were applied repeatedly on various groupings of the values of the covariates in order to find a scoring of the variables that gave rise to a satisfactory proportional hazards model for the data. For instance, a careful inspection of the estimated parameters for a number of various groupings of mitoses pointed at a logarithmic (base 10) scoring rather than the number themselves. In the same way thickness, level of invasion, and ulceration were regrouped from the initial detailed categories (Table 2) to the classes shown in Table 3. Likewise, less than 1 mm^2 of tumour tissue was seen to behave in the same way as 0 mitoses and was scored accordingly.

The prognostic significance of the covariates was tested by likelihood ratio tests and it was demonstrated that the importance of nuclear pleomorphism, nucleolar size, verrucous growth pattern, vascular invasion, pigmentation, solar elastosis, and histological type was insignificant. The spindle

Table 3. Estimates of β-parameters and their deviations for 1,195 patients treated with resection margin $\geqq 5$ cm. Also shown is the distributin of the patients on the categories of the covariates, and that of the number of deaths

Covariate (z)	No. of patients	No. of deaths	$\hat{\beta}$	SD($\hat{\beta}$)
Stage				
I	1,066	281		
II	112	72	0.688	0.146
III	17	16	1.119	0.277
Site				
trunk	496	196		
head and neck	19	6	−0.550	0.432
femur and upper arm	243	84	−0.099	0.138
crus and lower arm	402	70	−0.800	0.158
foot and hand	35	13	0.145	0.306
Thickness				
<1 mm	308	17		
1–1.99 mm	286	57	1.014	0.412
$\geqq 2$ mm	601	295	1.398	0.410
Ulceration				
0–4 mm	930	216		
5–9 mm	90	49	0.092	0.172
$\geqq 10$ mm	112	80	0.621	0.150
crusta	63	24	0.538	0.223
Mitoses per log (no. + 1)			0.987	0.174
Level[a]				
II	201	11		
III	549	136	0.037	0.454
IV A	218	85	0.325	0.476
IV B	155	86	0.529	0.479
V	72	51	0.592	0.498
Sex				
male	422	182		
Female	773	187	−0.225	0.121
Age per year			0.0111	0.0041
Cell type				
not spindle	1,146	358		
spindle	49	11	−0.906	0.331
Lymphocytic reaction per unit			−0.184	0.056
Regression				
no	1,025	327		
yes	170	42	1.140	0.507
Interactions				
<1 mm thick and regression	1,134	335		
1–1.99 mm thick and regression	37	10	−0.808	0.613
$\geqq 2$ mm thick and regression	24	24	−1.592	0.551
Total no. of patients	1,195			
Total no. of deaths		369		

[a] Level II ~ levels IIa + IIb; level III ~ levels IIIa + IIIb + IVa + IVb; level IV A ~ level IVc; level IV B ~ levels IVd + IVe + PM II; and level V ~ levels Va + Vb

cell type was of importance while the effect of nevoid and mixture was almost like the baseline level (i.e. epithelioid type). We therefore kept spindle cell in the analysis as a separate section but grouped together the other cell types. Levels of invasion were of importance ($p<0.009$) even though the effect of other variables including tumour thickness were accounted for by the model.

Of specific interest were melanomas with the deepest invasion of tumour cells along the hair follicles or sweat glands since tumour thickness may be measured in different ways for such melanomas. This question was investigated by including a covariate with the value 1 if the vertical distance from the epidermal granular cell layer to the deepest tumour cells in the papillary dermis around the skin appendages was greater than the tumour thickness measured without the consideration of these tumour cells, and 0 otherwise. The effect of this covariate was insignificant ($p>0.4$).

In the same way the effect of partial regression was shown to be insignificant. If, however, the interaction between partial regression and tumour thickness was considered, a strongly significant effect was discovered. Regression was a prognostically poor sign in melanomas <2 mm thick, especially in lesions <1 mm thick. In contrast, regression was a prognostically favourable sign in melanomas $\geqq 2$ mm thick.

The final analysis included 1,931 patients with complete information of the variables of significance. The number of patients (number of deaths) of the four groups of resection margin was $\geqq 5$ cm 1,195 (369), 2.1–4.9 cm 171 (75), 2.0 cm 301 (103), and 0.1–1.9 cm 264 (97). Equivalent results were obtained in the four groups. The results from the greatest group (i.e. resection margin $\geqq 5$ cm) are shown in Table 3. Table 3 shows that the following variables were found to possess prognostic significance even when adjusting for the effect of the other: clinical stage, site of tumour, tumour thickness, level of invasion, ulceration, mitotic activity, lymphocytic reaction, dominant type of tumour cell, regression, and the covariates for the interaction between regression and tumour thickness. The evaluation of the prognostic importance of sex and age of patient was uncertain, and both variables, therefore, were kept in the model.

Table 4 summarizes the characteristics of typical low, medium and high risk patients in stage I and the survival for such patients is shown in Fig. 1–4 for different widths of resection margin. As seen, no differences in survival in relation to resection margin are found for the low (A), medium (B) or high risk patients (C).

Together with the estimate of the underlying hazard function, $\lambda_0(t)$ or, equivalently, the estimate of the survival function, the estimates of β in Table 3 give the full description of the prognosis after malignant melanoma.

This enables the calculation of the actual estimate of the survival for an individual patient by the use of the numerical values of selected points of the survival function for a reference patient who in the present study is chosen to be a medium risk patient defined in Table 4. The survival values for such a patient are shown in Table 5. An example of the calculation is demonstrated below.

Table 4. Definition of a patient at low, medium and high risk

	Low risk patient	Medium risk patient	High risk patient
Clinical stage	I	I	I
Site of tumour	lower leg or lower arm	trunk	trunk
Tumour thickness (mm)	<1	1–1.99	$\geqq 2$
Ulceration (mm)	0	0	$\geqq 10$
Number of mitoses/mm^2	1	5	15
Level of invasion	II	III	V
Sex of patient	female	female	male
Age of patient (years)	45	45	45
Dominant tumour cell	spindle	not spindle	not spindle
Lymphocytic reaction	4	2	0
Partial regression	no	no	no

Table 5. Selected values of the survival function for a patient at medium risk treated with resection margin $\geqq 5$ cm

Years	Survival function	Years	Survival function
1	0.971	6	0.793
2	0.925	7	0.779
3	0.881	8	0.766
4	0.847	9	0.750
5	0.813	10	0.741

Denote by $S(t; \bar{Z})$ the survival function for the reference patient at medium risk with covariate vector $\bar{Z}$ as given in Table 4 and Table 6. The relation between the survival function $S(t; Z)$ for an individual patient with covariate vector Z and $S(t; \bar{Z})$ is given by the formula

$$S(t; Z) = \{S(t; \bar{Z})\}^{\exp\left\{\sum_{j=1}^{p} \beta_j (Z_j - \bar{Z}_j)\right\}}$$

where p is the number of covariates in the model, and $z = (z_1, \ldots, z_p)$, $\bar{z} = (\bar{z}_1, \ldots, \bar{z}_p)$.

Table 6 shows the calculation of $\sum \beta_j (z_j - \bar{z}_j)$ for an individual patient with the following characteristics: resection margin $\geqq 5$ cm, stage II, site crus or lower arm, thickness $\geqq 2$ mm, ulceration $\geqq 10$ mm, number of mitoses 10, level IV B, male aged 65, cell type spindle, lymphocytic reaction 3, and regression. In the column marked "characteristics" a * indicates to which group the patient belongs, and in the column "covariates" the corresponding values of the z's are shown.

The estimates of the β's ($\hat{\beta}$) are taken from Table 3, z's denote the characteristics of the individual patient, and $\bar{z}$'s denote the characteristics of the medium risk patient defined in Table 4.

Table 6. Calculation of $\sum \hat{\beta}_j (z_j - \bar{z}_j)$ for an individual patient with the covariate vector z by the $\hat{\beta}$'s (Table 3) and covariate vector $\bar{z}$ for a medium risk patient

Covariates	$\hat{\beta}$	Characteristics		Covariates		$\hat{\beta}(z-\bar{z})$
		individual patient	medium risk patient	z	$\bar{z}$	
Stage						
I		–	*			
II	0.688	*	–	1	0	0.688
III	1.119	–	–	0	0	0
Site						
trunk		–	*			
head and neck	−0.550	–	–	0	0	0
femur and upper arm	−0.099	–	–	0	0	0
crus and lower arm	−0.800	*	–	1	0	−0.800
foot and hand	0.145	–	–	0	0	0
Thickness						
<1 mm		–	–			
1–1.99 mm	1.014	–	*	0	1	−1.014
≧2 mm	1.398	*	–	1	0	1.398
Ulceration						
0–4 mm		–	*			
5–9 mm	0.092	–	–	0	0	0
≧10 mm	0.621	*	–	1	0	0.621
crusta	0.538	–	–	0	0	0
Log (mitoses + 1)	0.987	*	*	1.041	0.778	0.26
Level						
II		–	–			
III	0.037	–	*	0	1	−0.037
IV A	0.325	–	–	0	0	0
IV B	0.529	*	–	1	0	0.529
V	0.592	–	–	0	0	0
Sex						
male		*	–			
female	−0.225	–	*	0	1	0.225
Age per year	0.0111	*	*	65	45	0.222
Cell type						
not spindle		–	*			
spindle	−0.906	*	–	1	0	−0.906
Lymphocytic reaction per unit	−0.184	*	*	3	2	−0.184
Regression						
no		–	*			
yes	1.140	*	–	1	0	1.140
Interactions						
<1 mm thick and regression		–	–			
1–1.99 mm thick and regression	−0.808	–	–	0	0	0
≧2 mm thick and regression	−1.592	*	–	1	0	−1.592
Total, $\sum \hat{\beta}_j (z_j - \bar{z}_j)$						0.550

In Table 5 it is seen that the 5 and 10 year survival for the medium risk patient is 0.813 and 0.741, respectively. Therefore the 5 year survival for the above-mentioned individual patient is (as $\exp(0.550) = e^{0.550} = 1.733$) $\hat{s}(5; z) = 0.813^{1.733} = 0.698 = 69.8\%$, and the 10 year is $\hat{s}(10; z) = 0.741^{1.733} = 0.595 = 59.5\%$.

Discussion

In the present study four groups of size of resection margin (<2 cm, 2 cm, 2.1–4.9 cm, and ≧5 cm) were analysed separately. The multivariate regression analyses show that the following variables are *independent risk factors* (i.e. risk factors even when adjusting for all other factors): clinical stage, site of tumour, tumour thickness, level of invasion, mitotic activity, ulceration, lymphocytic reaction, type of dominant invasive tumour cell, and partial regression. When accounting for these factors the following variables do not influence prognosis significantly; histological type of melanoma, nuclear pleomorphism, nucleolar size, vascular invasion, pigmentation, dermal elastosis, and verrucous growth pattern. In the present analyses the prognostic importance of sex and age is uncertain and will be further investigated in a later paper.

Clinical stage and site of tumour were shown to be important prognostic factors by Olsen (1966) a finding corroborated by others (Eldh et al. 1978, Balch et al. 1979, Liestøl et al. 1982, Schmoeckel et al. 1983, Rogers et al. 1983). The present study supports this finding even when adjusting for a great number of other clinico-pathological variables. Tumours located on lower leg and arm are associated with the best survival, followed by those located on head and neck, and then by those situated on thigh, upper arm, trunk, foot and hand. Only the sites on lower leg and lower arm, however, possess significant influence on prognosis ($p < 0.0001$).

Level of invasion and tumour thickness are associated with the capability of the tumour to penetrate the different layers of the skin (Clark et al. 1969) and tumour volume (Breslow 1970), respectively. The present study supports the previously reported improvement of the Clark staging system (Søndergaard 1985) and shows both levels of invasion and tumour thickness to be risk factors even when adjusting for the other risk factors. The tumor thickness does not eliminate the prognostic influence of levels of invasion.

Also Roger et al. (1983) found level of invasion to be an independent risk factor in their analysis of 971 patients, as did Liestøl et al. (1982). Liestøl et al. (1982), however, did not include tumour thickness among the variables investigated.

In 153 out of 2,012 melanomas the deepest tumour cells were situated in the papillary dermis around hair follicles and sweat glands. In accordance with Breslow (1976 and 1977) such tumour cells were not used in the measurement of thickness. The practice is supported by the present study.

Differentiation between verrucous and non-verrucous lesions is found to be prognostically insignificant.

Mitotic activity, nuclear pleomorphism, and nucleolar size are prognostically significant factors ($p < 0.00001$) when employed alone. These characteristics have been shown to correlate with frequency of DNA heteroploidy in malignant melanomas (Søndergaard et al. 1983). The effect of nuclear pleomorphism and nucleolar size is, however, found to be secondary to mitotic activity.

The finding that mitotic activity acts as an independent risk factor is in accordance with some studies (Eldh et al. 1978; Esch et al. 1981; Prade et al. 1982; Day et al. 1982; Schmoeckel et al. 1983), but in contrast to others (McGovern et al. 1979; Drzewiecki and Andersen 1982; Liestøl et al. 1982; Rogers et al. 1983). Such divergenicies may be due to differences in the scoring employed, the area investigated, and the the quality of the histological material examined.

Ulceration is presumably correlated with rapid tumour growth like great mitotic activity. Mitotic activity might, therefore, render the recording of ulceration superfluous and vice versa. In accordance with most investigations, we recognize both ulceration and mitotic activity as independent risk factors (Eldh et al. 1978; Esch et al. 1981; Prade et al. 1982; Day et al. 1982; Schmoeckel et al. 1983).

Increasing lymphocytic reaction beneath the invasive part of the tumour was found to act as a favourable independent risk factor in accordance with some other studies (Drzewiecki and Andersen 1982; Day et al. 1982; Schmoeckel et al. 1983). Lymphocytic reaction may thus be a valuable parameter of host defence.

The spindle type of invasive tumour cell is found as a favourable independent determinant of survival.

Histological type of melanoma is thought to differentiate between melanomas of different biological behaviour (Clark et al. 1969; McGovern et al. 1973 and 1980; Elder et al. 1979; Søndergaard 1983A). When adjusting for the factors in the present study, histological type is of no prognostic significance. This is in accordance with other investigations (Eldh et al. 1978; Balch et al. 1979; Esch et al. 1981; Drzewiecki and Andersen 1982; Liestøl et al. 1982; Prade et al. 1982; Day et al. 1982; Schmoeckel et al. 1983; Rogers et al. 1983).

In the present study acral lentiginous melanomas (ALM) (Reed 1976) were classified as SSM in accordance with the classification proposed at the Cancer Conference in Sydney (McGovern et al. 1973). No difference has been demonstrated between the prognosis associated with SSM and ALM (Søndergaard and Olsen 1980; Søndergaard 1983B).

Vascular invasion, pigmentation and dermal elastosis are of no prognostic significance when other clinico-pathological characteristics are accounted for in accordance with most other investigations (Eldh et al. 1978; Esch et al. 1981; Drzewiecki and Andersen 1982; Liestøl et al. 1982; Prade et al. 1982).

Partial regression is an independent risk factor, which, however, interacts with tumour thickness. As seen from Table 3 regression is a prognostically poor sign in melanomas <2 mm thick, especially in lesions <1 mm thick. In contrast, it is a prognostically favourable sign in lesions $\geqq 2$ mm. This presumably is explained by tumour regression being a favourable defence mechanism, which on the other hand may interfere with the grading of other histological variables.

In conclusion our results show that an optimal prognostic model must be multifactorial. Apart from clinical stage and site of tumour it must include variables grading volume and cellular malignancy of tumour, (tumour thickness, ulceration, mitotic rate, dominant cell type, infiltrative ability) and indicators of host defence (lymphocytic reaction, regression).

An important use of the knowledge of the independent risk factors and their relative significance is the estimation of survival for individual patients with malignant melanoma of the skin.

Acknowledgements. This study was supported by grants from the Danish Cancer Society (project number 59/77) and the Danish Medical Research Council (project number 512-20346). The authors wish to thank Dr. K. Hou-Jensen for initiating for the project and for valuable suggestions, P.K. Andersen, the Statistical Research Unit, for helpful discussions on the statistical analysis, and Dr. G. Olsen, Dr. H. Johansen, and Dr. O. Møller Jensen for their great help. We are greatful to the departments of pathology of the following hospitals for lending histological slides: Sundby Hospital, Bispebjerg Hospital, Københavns Kommunehospital, Hvidovre Hospital, Rigshospitalet, KAS Gentofte, KAS Herlev, KAS Glostrup, Hillerød Centralsygehus, Slagelse Centralsygehus, Holbæk Centralsygehus, Frederiksberg Hospital, Nœstved Centralsygehus, Nykøbing Falster Centralsygehus, Roskilde Amtssygehus, Odense Sygehus, Svendborg Sygehus, Aarhus Kommunehospital, Aarhus Amtssygehus, Aalborg Sygehus, Holstebro Centralsygehus, Hjørring Sygehus and Vejle Sygehus.

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Accepted January 22, 1985