Virchows Arch [Pathol Anat] (1985) 408:249–258

Virchows Archiv A

Therapeutic and clinico-pathological factors in the survival of 1,469 patients with primary cutaneous malignant melanoma in clinical stage I

A multivariate regression analysis

Knud Søndergaard[1] **and Geert Schou**[2,3]
[1] Department of Pathology, The Finsen Institute, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
[2] Statistical Research Unit, Danish Medical and Social Science Research Councils
[3] Danish Cancer Registry, Institute of Cancer Epidemiology, under the Danish Cancer Society, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

Summary. Therapeutic and clinico-pathological data of 1,469 patients with clinical stage I malignant melanoma of the skin without histological evidence of fibrotic areas of regression were examined by multivariate regression analysis. In accordance with a previous analysis anatomical site of tumour, tumour thickness, level of invasion, mitotic rate, ulceration, lymphhocytic reaction, dominant type of invasive tumour cell, and sex were found to act as independent risk factors. The present analysis, furthermore, showed that size of resection margin, diagnostic biopsy, removal of the deep fascia, age at surgery, as well as presence and depth of nevus cells did not influence prognosis when adjusting for the independent risk factors.

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

Introduction

In a previous study (Søndergaard and Schou 1985) in which 1,931 patients were included it was shown that independent factors influencing survival after malignant melanoma of the skin included clinical stage, anatomical site of tumour, tumour thickness, level of invasion, mitotic rate, ulceration, lymphocytic reaction, predominant type of invasive tumour cell, and histological evidence of partial regression. Due to inhomogeneity the data material had to be grouped into 4 subgroups according to size of resection margin (< 2 cm, 2 cm, 2.1–4.9 cm, and ≥ 5 cm) in order to evaluate the prognostic effect of non-therapeutic characteristic. This grouping, however, prevented evalution of the prognostic effect of the size of resection

Offprint request to: K. Søndergaard

margin, and made the evaluation of the variables sex and age at operation uncertain.

The purpose of the present study was to examine in more detail the influence on survival after malignant melanoma of the therapeutic variables size of resection margin, previous biopsy and depth of resection as well as the variables presence and depth of histologically benign nevus cells and sex and age of patient.

In the present analysis only patients in clinical stage I were included in order to make the data material more homogeneous. For the same reason cases were excluded if fibrotic areas of regression could be found histologically, since regression may influence the grading of other histological variables. By doing so, all the variables could be analysed in a single Cox model.

Material and method

The histological material from 2,012 patients with malignant melanoma seen at the Finsen Institute during the period 1949–1978 was available and suitable for microscopic reclassification, which was done by one person (K.S.). The patients were treated by complete surgical excision as described by Olsen (1966, 1970). The extent of the excision varied during the period although it most often was 5 cm (Table 1). In the face, sole and palm a margin of 2 cm was employed rather than 5 cm. The excision went down to, but did not include the deep fascia. As a rule regional lymph nodes were not removed prophylactically. The fascia, however, was removed in a number of cases and elective regional lymph node dissection (*ERND*) was sometimes performed. Melanomas on the fingers and toes were commonly treated be exarticulation in the metacarpo and metatarsophalangeal joint. Local recurrences and metastases to the skin and lymph nodes were treated primarily by surgery. The patients were followed up at the Finsen Institute serveral times a year for the first years and later once a year for up to 10 years or more.

If histologically benign nevus cells were found in the tumour their depth (*"nevus thickness"*, *NT*) was measured in mm to 2 decimal places by an ocular micrometer as the maximal vertical distance from the top of the epidermal granular cell layer to the deepest nevus cells. In ulcerated lesions the most superficial melanoma cells were used instead of the missing granular cell layer.

Table 1. Size of resection margin for 1,469 patients

Size of resection (cm)	Number of patients
0.1–0.4	41
0.5	42
0.6–0.9	12
1.0	64
1.1–1.5	43
1.6–1.9	0
2.0	225
2.1–2.9	14
3.0	82
3.1–4.9	25
5.0	911
>5.0	10
Total	1469

Table 2. Definition of a patient at low, medium and high risk

	Low risk patient	Medium risk patient	High risk patient
Sex	female	female	male
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
Dominant tumour cell	spindle	not spindle	not spindle
Lymphocytic reaction	4	2	0

Nevus cells in the papillary dermis around skin appendages were avoided. The other histological variables were graded as previously described (Søndergaard and Schou 1985).

Restricting the material to patients with cutaneous melanoma in clinical stage I and without histological sign of fibrotic areas of regression, 1,469 patients were available for analysis. These patients had complete information regarding sex, age of patients at final surgery, dates of previous biopsy and final surgery, size of final resection margin, clinical follow up, anatomical site of tumour, tumour thickness, level of invasion, number of mitoses per mm^2, size of ulceration, lymphocytic reaction, type of dominant invasive tumour cell, and presence and depth of benign nevus cells in tumour.

Table 1 shows size of resection margin for 1,469 patients. As seen, the sizes of resection margins naturally fell into 4 subgroups, which were 0.1–1.9 cm (202 patients), 2.0 cm (225 patients), 2.1–4.9 cm (121 patients) and 5.0 cm or more (921 patients).

Partial diagnostic biopsy was performed in 95 patients and complete biopsy in 384 patients. The partial biopsy was followed by complete excision of the melanoma within 3 weeks in 71%, within 7 weeks in 91% and within 4 months in 97%, respectively. The complete biopsy was followed by final excision in 87% and 96% of the cases within 3 weeks and 2 months, respectively.

The statistical method used was the semiparametric regression analysis introduced by Cox (1972) applied on the time from radical surgery until death from malignant melanoma. The model states that the death rate $\lambda(t; Z_i)$ for the i'th patient at time t after surgery is given as an underlying (common) death rate $\lambda_o(t)$ multiplied by an exponential function of the covariate vector Z_i specific for the i'th patient:

$$\lambda(t; Z_i) = \lambda_o(t) \exp \{\beta_1 Z_{i1} + \ldots + \beta_p Z_{ip}\}.$$

Here $\lambda_o(t)$ is the unknown and unspecified death rate for a reference patient for whom the covariate vector Z_i equals zero, and $\beta_1,\ldots,\beta_p$ are the unknown parameters to be estimated. A β significantly different from 0 indicates that the corresponding variate has prognostic significance. The reference patient is characterized in Table 2 as the one of medium risk. In order to find an appropriate scoring of the covariates the graphical goodness-of-fit tests described by Andersen (1982) were performed. 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-square distribution.

Results

The statistical analysis showed that the following factors are independent risk factors, i.e. they are of prognostic importance even when adjusting for the other factors (the p-values are test probabilities for the omission of the

Table 3. Removal of the deep fascia correlated with site of tumour and size of resection margin in 637 patients with stage I melanoma of extremities exclusive foot and hand and without regression

Site of tumour	Fascia removed	Size of resection margin				Total	
		<2 cm	2 cm	2.1–4.9 cm	≧5 cm	No.	%
Upper limb	yes	2	4	0	0	6	3
	no	14	8	7	138	167	97
Lower limb	yes	3	7	10	3	23	5
	no	25	17	17	382	441	95
Upper and lower limbs	yes	5	11	10	3	29	5
	no	39	25	24	520	608	95
Total		44	36	34	523	637	100

variate). Sex ($p < 0.002$), site of lesion ($p < 0.0001$), tumour thickness ($p < 0.0001$), ulceration ($p < 0.001$), mitotic rate ($p < 0.0001$), level of invasion ($p < 0.002$), type of dominant invasive tumour cell ($p < 0.0001$) and lymphocytic reaction ($p < 0.001$). When accounting for the independent risk factors the following variables did not influence survival: age of patients ($p = 0.6$), a crust without ulceration ($p = 0.2$), previous partial biopsy ($p = 0.3$), previous complete biopsy ($p = 0.1$) and size of resection margin ($p = 0.4$).

The analysis also showed that the female superiority in survival was the same in 3 age groups (less than 45 years, 45–54 years, more than 54 years) when adjusting for the other risk factors ($p = 0.2$).

Histologically benign nevus cells were found in 135 out of 1,469 patients. In 82 patients the nevus thickness (*NT*) was greater than the tumour thickness (*TT*). By including a covariate with the value 1 if benign nevus cells were seen and O if not, it was found that the presence of nevus cell was not an independent risk factor ($p = 0.6$). In the same way it was found that the survival was not influenced by NT being greater than TT ($p = 0.6$).

Elective regional lymph node dissection (*ERND*) was performed in 34 of 1,469 patients. No statistically significant relationship was found between ERND and size of resection margin ($x^2 = 2{,}67$, d.f. $= 3$, $p = 0.5$)

In 5 out of 642 melanomas located on the extremities except for feet and hands it was uncertain whether or not the excision of tumour included the deep fascia. In 29 out of the remaining 637 patients the surgery included the deep fascia (Table 3). A covariate was included with the value 1 if the fascia was removed and O otherwise. By Cox regression analysis of the 637 patients it was found that the removal of the fascia did not influence survival when adjusting for the above mentioned independent risk factors ($p = 0.6$).

In Table 4 is given a summary of the result of the estimation of the β's as well as the number of patients with the various values of the covariates.

Table 4. Estimates of β-parameters and their standard deviations in the Cox model. Also shown is the distribution of the 1,469 patients in the categories of the covariates, and the number of deaths

Covariates (Z)	No. of patients	No. of deaths	$\hat{\beta}$	SD ($\hat{\beta}$)
Sex				
male	480	188	–	–
female	989	236	– .338	.109
Site				
Trunk	431	167	–	–
Head and neck	270	73	– .208	.148
Femur and upper arm	230	69	– .205	.150
Crus and lower arm	412	69	– .858	.155
Foot and hand	126	46	– .191	.180
Tumour thickness				
> 1 mm	359	12	–	–
1–1.99 mm	352	67	.937	.358
≧ 2 mm	758	345	1,301	.357
Ulceration				
0– 4 mm	1,226	286	–	–
5– 9 mm	129	65	.106	.149
≧10 mm	114	73	.545	.143
Mitoses				
Per log (no. + 1)	–	–	1,150	.154
Level				
II	228	5	–	–
III	640	150	.529	.526
IVA	316	123	.806	.538
IVB	183	87	.897	.544
V	102	59	1.209	.553
Cell type				
Not spindle	1,349	398	–	–
Spindle	120	26	– .682	.211
Lymphocytic reaction				
Per unit	–	–	– .221	0.054
Total no. of patients	1,469			
Total no. deaths		424		

As previously described (Søndergaard and Schou 1985) the survival function of a given patient can be calculated from Cox model using the values of $\hat{\beta}$ (Table 4) and the selected values of the survival function (Table 5) for the reference patient (the medium risk patient of Table 2).

In Fig. 1 is given examples of survival functions for a patient at low risk (L), medium risk (M), and high risk (H), as defined in Table 2.

Table 5. Selected values of the survival function for the *reference* (medium risk) *patient*

Years after surgery	Survival function
1	.975
2	.922
3	.878
4	.841
5	.799
6	.780
7	.761
8	.740
9	.723
10	.709

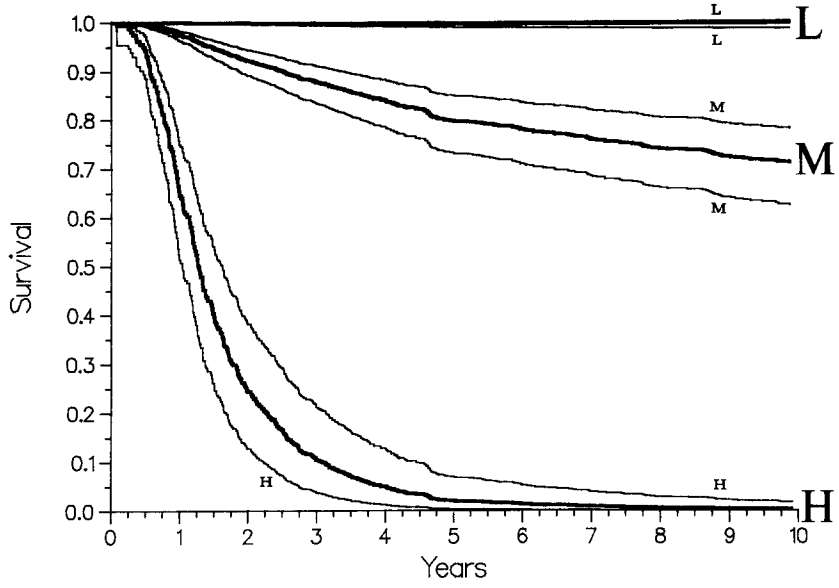

Fig 1. Survival functions for a patient at low (*L*), medium (*M*), and high risk (*H*). By *L*, *M*, and *H* are indicated the 95% confidence limits for the survival functions *L*, *M*, and *H*

Discussion

From the present study it appeared that sex was an independent risk factor in contrast to the age of the patient. It was also seen that the better prognosis for females was not correlated with their age when adjusting for the other independent risk factors. Thus female climacteric status as such seems to have no influence on survival after melanoma. Neither did the presence and depth of nevus cells influence survival, when adjusting for the other independent risk factors. Therefore histologically benign nevus cells should be ignored when measuring tumour thickness.

There are different views as to whether or not biopsy before final surgery is acceptable (Olsen 1966; Harris and Gumport 1975; Cady 1975; Davis 1976; Epstein et al. 1969; Lee 1974; Cochran 1976; Encke and Best 1976;

Mattson et al. 1976; Eldh 1979; Drzewiecki et al. 1980). The problem has been examined in one Cox regression analysis (Drzewiecki and Andersen 1982), which showed that prognosis was slightly improved by previous biopsy. In contrast, the present study showed that partial or complete previous biopsy did not influence survival rate when comparing melanomas characterized by the same independent risk factors, i.e. melanomas of otherwise equal prognosis.

In accordance with most authors (Olsen 1966; Ackerman and Su 1979; Milton and Shaw 1983), however, it is recommended that lesions suspected of being malignant melanomas are excised in toto when possible in order to obtain optimal specimens for histological diagnosis and grading of malignancy.

In general, wide surgical excision of cutaneous melanoma in clinical stage I has been advocated, commonly with a resection margin of 5 cm beyond the periphery of the lesion when feasible. By various clinico-pathological staging systems it has been possible to estimate the clinical course of melanoma (Eldh et al. 1978; Esch et al. 1981; Drzewiecki and Andersen 1982; Prade et al. 1982; Day et al. 1982/a l.c.; Schmoeckel et al. 1983/a l.c.; Rogers et al. 1983; Søndergaard and Schou 1985). The extensive resection margins, in consequence, have been recommended to be reduced in low risk melanomas based on different staging systems (Breslow and Macht 1977; Balch et al. 1979; Cascinelli et al. 1980; Rampen 1981; Day et al. 1982/b l.c.; Schmoeckel et al. 1983/b l.c.; Elder et al. 1983). In the present analysis of 1,469 patients with melanomas treated with a wide range of sizes of resection margin the size of the resection margin did not influence survival rate when adjustment was made for the identified relevant prognostic factors, i.e. when comparing melanomas of otherwise equal prognosis.

It cannot be excluded that "benign" looking lesions were treated with smaller resection margins more frequently than were more "malignant" looking ones. The influence on survival of such subjective clinical indications is undoubtly minimal since factors which might have influenced the choice of treatment were accounted for by the Cox model. Sex and age of patient were thus accounted for directly and so was site of tumour, size of resection margins, previous biopsy and ulceration. Rapidly growing elevated lesions were indirectly accounted for by tumour thickness, mitotic rate, dominant type of tumor cell and level of invasion.

The present findings thus support the conclusion of Ackerman and Scheiner (1983), that surgery of melanomas of any thickness should merely aim to remove all neoplastic melanocytes in the local process. The finding that narrow excision does not adversely affect survival when comparing melanomas with the same characteristics is in accordance with Drzewiecki's demonstration (1979) of activated melanocytes and suspicious cells by dopa-staining only in the immediate vicinity (a few mm to one cm) of the lesion.

Olsen (1966) showed elective regional lymph node dissection (ERND) to be of no benefit, if nodes were dissected when palpable alterations were noted, which was practiced in the present material. The frequency of ERND in the present study varied from 1–2% to 4% in different sites of tumour,

different groups of thickness, and different groups of resection margin. The differences were not statistically significant. Due to the small number of patients treated by ERND, the prognostic influence of this procedure could not be evaluated in the Cox analysis. Two randomized studies of 553 and 173 patients, respectively (Veronesi et al. 1977; Sim et al. 1978) have not demonstrated any influence of ERND on survival. Day et al. (1982/a l.c.), however, concluded that a greater number of patients is required to detect statistical significance of ERND, should it exist. In a regression analysis of 177 patients with melanomas which were 1.51–3.99 mm thick Day et al. (1982/a l.c.) found that tumours located at the lower leg and lower arm had a favourable prognosis. Since the excision of 90% of the melanomas on these sites was supplemented by ERND, they suggested that ERND might be responsible for the good prognosis. The present study does not support this suggestion, since tumours located on lower leg and lower arm also had a favorable survival, although the number of ERND treated cases was negligible (2% in those sites).

A constant and continuous fascia is almost only found on the extremities (except for feet and hands) (Olsen 1966; Milton and Shaw 1983). In the present study the fascia was removed in 29 out of 637 stage I melanomas without regression changes on the extremities (except feet and hands) (Table 3). A Cox analysis on the 637 patients showed that the removal of the fascia had no influence on survival when adjusted for the other risk factors.

In conclusion, we found that factors which independently influence survival for patients with melanoma in clinical stage I without fibrotic areas of partial regression were sex, site of lesion, tumour thickness, ulceration, mitotic rate, level of invasion, type of dominant invasive tumour cell and lymphocytic infiltration. An optimal prognostic model must thus be multifactorial. When measuring tumour thickness histologically benign nevus cells should be ignored, and the size of resection margin, removal of deep fascia and previous biopsy do not influence survival.

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 grateful 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, Næstved Centralsygehus, Nykøbing Falster Centralsygehus, Roskilde Amtssygehus, Odense Sygehus, Svendborg Sygehus, Aarhus Kommunehospital, Aarhus Amtssygehus, Aalborg Sygehus, Holstebro Centralsygehus, Hjørring Sygehus and Vejle Sygehus.

References

Ackerman AB, Scheiner AM (1983) How wide and deep is wide and deep enough? A critique of surgical practice in excisions of primary cutaneous malignant melanoma. Hum Pathol 14: 743–744

Ackerman AB, Su WPD (1979) The histology of cutaneous malignant melanoma. In: Kopf AW, Bart RS, Rodriquez-Sains RS, Ackerman AB (eds) Malignant melanoma. Masson Publishing USA, Inc, New York, pp 135–136

Andersen PK (1982) Testing goodness of fit of Cox's regression and life model. Biometrics 38:67–77

Balch CM, Murad TM, Soong S-J, Ingalls AL, Richards PC, Maddox WA (1979) Tumor thickness as a guide to surgical management of clinical stage I melanoma patients. Cancer 43:883–888

Breslow A, Macht SD (1977) Optimal size of resection margin for thin cutaneous melanoma. Surg Gynecol Obstet 145:691–692

Cady B (1975) Changing concepts in malignant melanoma. Med Clin N Amer 59:301–308

Cascinelli N, Esch EP van der, Breslow A, Morabito A, Bufalino R (1980) Stage I melanoma of the skin: the problem of resection margins. Eur J Cancer 16:1079–1085

Cochran AJ (1976) The biology and treatment of malignant melanoma. Eur J Cancer 12: 585–594

Cox DR (1972) Regression models and life tables (with discussion). J Roy Statist Soc B 34: 187–220

Davis NC (1976) Cutaneous melanoma: The Queensland experience. In: Ravitch MM, Austen WG, Scott HW, Fonkalsrud EW, Polk HC, Steichen FM (eds) Current problems in surgery. Year book medical publishers, Inc., Chicago, p 25

Day CL, Mihm MC, Lew RA, Harris MN, Kopf AW, Fitzpatrick TB, Harrist TJ, Colomb FM, Postel A, Hennessey P, Gumport SL, Raker JW, Malt RA, Cosimi AB, Wood WC, Roses DF, Gorstein F, Rigel D, Friedman RJ, Mintzis MM, Sober AJ (1982/a l.c.). Prognostic factors for patients with clinical stage I melanoma on intermediate thickness (1.51–3.99 mm). A conceptual model for tumor growth and metastasis. Ann Surg 195:35–43

Day CL, Mihm MC, Sober AJ, Fitzpatrick TB, Malt RA (1982/b l.c.) Narrower margins for clinical stage I malignant melanoma. N Engl J Med 306:479–482

Drzewiecki KT (1979) The epidermal melanocyte system in patients with malignant melanoma. Quantitative and qualitative investigations of dopa positive melanocytes. Scand J Plast Reconstr Surg 13:333–339

Drzewiecki KT, Andersen PK (1982) Survival with malignant melanoma. A regression analysis of prognostic factors. Cancer 49:2414–2419

Drzewiecki KT, Ladefoged C, Christensen HE (1980) Biopsy and prognosis for cutaneous malignant melanoma in clinical stage I. Scand J Plast Reconstr Surg 14:141–144

Elder DE, Guerry D, Heiberger RM, LaRossa D, Goldman LI, Clark WH, Thompson CJ, Matozzo I, Horn MV (1983) Optimal resection margin for cutaneous malignant melanoma. Plast Reconstr Surg 71:66–72

Eldh J (1979) Excisional biopsy and delayed wide excision versus primary wide excision of malignant melanoma. Scand J Plast Reconstr Surg 13:341–345

Eldh J, Boeryd B, Peterson LE (1978) Prognostic factors in cutaneous malignant melanoma in stage I. A clinical morphological and multivariate analysis. Scand J Plast Reconstr Surg 12:243–255

Encke A, Best A (1976) Die Chirurgische Behandlung des Melanomas. Lagenbecks Arch Chir 342:527–532

Epstein E, Bragg K, Linden G (1969) Biopsy and prognosis of malignant melanoma. J Am Med Ass 208:1369–1371

Esch EP van der, Cascinelli N, Preda F, Morabito A, Bufalino R (1981) Stage I melanoma of the skin: evaluation of prognosis according to histologic characteristics. Cancer 48: 1168–1673

Harris MN, Gumport SL (1975) Biopsy technique for malignant melanoma. J Derm Surg 1:24–27

Kalbfleisch JD, Prentice RL (1980) The statistical analysis of failure data. Wiley, New York

Lee Y-T N (1974) Malignant melanoma: To biopsy or not to biopsy. CA 24:104–105

Mattson W, Gynning I, Hogeman KE, Jacobsson S, Linell F (1976) A retrospective study of 304 cases of malignant melanoma in Malmoe 1952–71. Scand J Plast Reconstr Surg 10:189–195

Milton GW, Shaw HM (1983) Surgical approaches to melanoma. Pigment Cell 6:166–186

Olsen G (1966) The malignant melanoma of the skin. New theoris based on a study of 500 cases. Thesis Acta Chir Scand Suppl 365

Olsen G (1970) Some views on the treatment of melanomas of the skin. Arch Chir Neerl 22-2:79–90

Prade M, Bognel C, Charpentier P, Gadenne C, Duvillard P, Sancho-Garnier H, Petit J-Y (1982) Malignant melanoma of the skin. Prognostic factors derived from a multifactorial analysis of 239 cases. Am J Dermatopathol 4:411–412

Rampen F (1981) Melanoma of the skin: The problem of resection margins. Eur J Cancer 17:589–590

Rogers GS, Kopf AW, Rigel DS, Friedman RJ, Levine JL, Levenstein M, Bart RS, Mintzis MM (1983) Effect of anatomical location on prognosis in patients with clinical stage I melanoma. Arch Dermatol 119:644-649

Schmoeckel C, Bockelbrink A, Bockelbrink H, Braun-Falco O (1983/a l.c.) Low- and high-risk malignant melanoma-II. Multivariate analyses for a prognostic classification. Eur J Cancer Clin Oncol 19:237–243

Schmoeckel C, Bockelbrink A, Bockelbrink H, Kistler H, Braun-Falco O (1983/b l.c.) Low and high-risk malignant melanoma-III. Prognostic significance of the resection margin. Eur J Cancer Clin Oncol 19:245–249

Sim FH, Taylor WF, Ivins JC, Pritchard DJ, Soule EH (1978) A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma. Preliminary results. Cancer 41:948–956

Søndergaard K, Schou G (1985) Survival with primary cutaneous malignant melanoma evaulated from 2,012 cases. A multivariate regression analysis. Virchows Arch A 406:179–195

Veronesi U, Adamus J, Bandiera DC, Brennhovd IO, Cacers E, Cascinelli N, Claudio F, Ikonoisov RL, Javorskj VV, Kirov S, Kulakowski A, Lacour J, Lejeune F, Mechl Z, Morabito A, Rode I, Sergeev S, Slooten E van, Szczygiel K, Trapeznikov NN, Wagner RI (1977) Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. N Engl J Med 297:627–630

Accepted August 3, 1985