Virchows Arch [Pathol Anat] (1985) 408:241–247

Virchows Archiv A

Partial regression in thin primary cutaneous malignant melanomas clinical stage I

A study of 486 cases

Knud Søndergaard and Klaus Hou-Jensen

Dempartment of Pathology, Finsen Institute, Rigshospitalet, Blegdamsvej 9, Dk-2100 Copenhagen, Denmark

Summary. 486 patients with primary cutaneous malignant melanoma clinical stage I were examined in order to evaluate the prognostic importance of partial regression in thin lesions. All the melanomas measured 1 mm or less in maximal thickness. The study showed that past regression with fibrotic scar tissue adversely affected survival in patients with thin melanomas. The 10 year survival was 95% for patients without regression in contrast to 79% for patients with past regression. It was, furthermore, demonstrated that active regression without fibrotic scar tissue did not influence survival significantly.

The wider and the thicker the fibrotic area, the poorer the survival. Although the prognostic importance of this finding was not statistically significant, we suggest that the horizontal width of the fibrotic area in particular may be a valuable prognostic guide in thin melanomas with past regression.

Key words: Malignant melanoma – Cutaneous – Thin – Regression

Indroduction

Breslow demonstrated in 1970 and 1975 that melanomas measuring less than 0.76 mm in thickness were correlated with an excellent prognosis. Some studies, however, showed that thin melanomas with histological signs of regression metastasized more frequently than did thin melanomas without regression (Gromet et al. 1978; Paladugu and Yonemoto 1983). Other studies did not support this finding (Trau et al. 1983; McGovern et al. 1983; Briggs et al. 1984).

486 patients with clinical stage I melanomas with tumour thickness of 1 mm or less were examined in order to evaluate the influence of regression on the long term survival. Furthermore, the prognostic importance of the phase and the extension of regression was examined.

Offprint requests to: K. Søndergaard at the above address

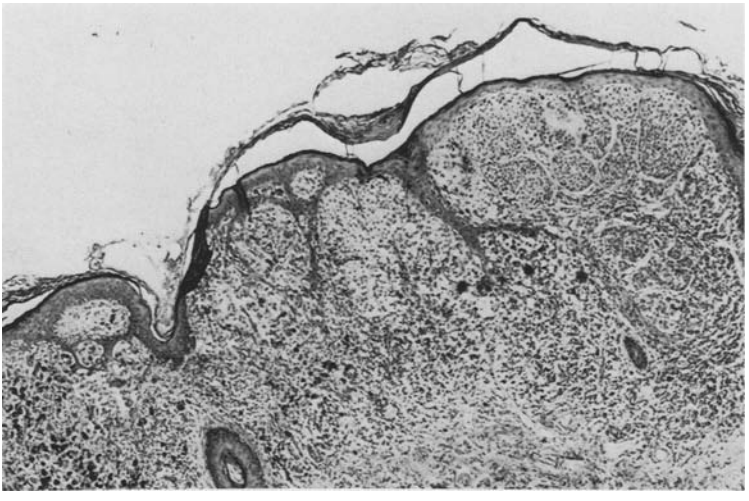

Fig. 1. Thin malignant melanoma with slight active regression. Haematoxylin and eosin. × 50

Material and method

The study included 486 patients with primary cutaneous malignant melanoma in clinical stage I measuring 1 mm or less in tumour thickness. The patients were part of 2012 melanoma patients seen at the Finsen Institute from 1949 til 1978 with available and suitable histological material from the primary lesion.

The histological sections were stained with haematoxylin and eosin, and the histological classification was done by one of us (K.S.). The study included no patients with in situ melanoma (Clark's level I) or with completely regressed lesions.

The lesions were treated by complete surgical excision and the patients were followed up for 10 years or more as previously described (Søndergaard and Schou 1985).

The histological examination included. A) *Partial regression,* which was graded as follows:

1. *No regression.*

2. *Slight active regression* defined as areas in the lesion with lymphocytic infiltration among the tumour cells which showed degenerative features and slight to moderate loss of cells (Fig. 1).

3. *Marked active regression* defined as areas with severe lymfocytic reaction and marked loss of tumour cells.

4. *Past regression* defined as a scar with fibrosis, a variable number of lymphocytes, melanophages, new blood vessels and possible few tumour cells (McGovern 1975) (Fig. 2).

In all cases with past regression the maximal horizontal width and the maximal vertical thickness of the fibrosis was measured in mm by ocular micrometer (Fig. 2). The thickness of the fibrosis was measured from the top of the epidermal granular cell layer. If both active and past regression were found in the same lesion only past regression was recorded.

B) *Other histological variables* included tumour thickness, level of invasion, mitotic activity, ulceration, dominant type of tumour cell, and lymphocytic reaction beneath the part of tumour without regression. They were graded as previously described (Søndergaard and Schou 1985).

The clinical information included the age and sex of patient, clinical stage, site of tumour, size of resection margin, and clinical course.

Statistical analysis: The cumulative survival rates were calculated by the life table method and compared by the logrank test (Peto et al. 1977). Where appropriate chi square test and the Student t-test were used. Significance was assessed at $p < 0.05$.

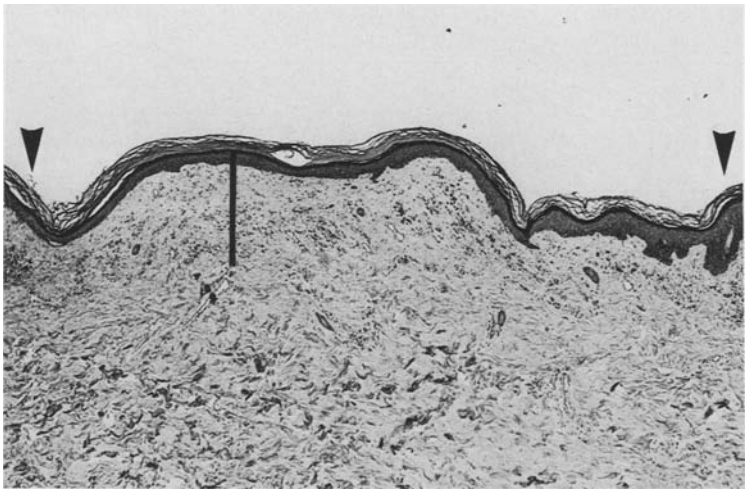

Fig. 2. Thin malignant melanoma with past regression. The *vertical line* indicates the thickness of fibrosis. The horizontal width of fibrosis is shown by 2 *arrows*. Haematoxylin and eosin. ×30

Table 1. Relationship between width and thickness of the fibrosis in 122 melanomas with sign of past regression

Vertical thickness of fibrosis (mm)	Horizontal width of fibrosis (mm)			
	0.6–2.5	2.6–4.0	>4.0	Total
0.1	0	0	0	0
0.2	13	5	1	19
0.3	20	8	9	37
0.4	11	8	10	29
0.5	11	4	3	18
0.6	3	0	3	6
0.7–0.8	5	2	2	9
0.9–1.0	2	1	1	4
>1.0	0	0	0	0
	65	28	29	122

Results

Of 486 clinical stage I melanomas ≦1 mm thick 213 (44%) showed no regression, 85 (17%) slight active regression, 66 (14%) marked active regression, and 122 (25%) past regression.

Table 1 shows the maximal width and thickness of the fibrotic area in 122 lesions with past regression. There was a certain tendency for great width of fibrosis to be associated with greater thickness. The range in fibrotic thickness was, however, small and in 84% of the cases (103/122) the fibrotic thickness was ≦0.5 mm.

Table 2. Partial regression related to various clinical and pathological characteristics in 486 patients with clinical stage I melanoma ≦1 mm thick

	Regression			
	None	Slight active	Marked active	Past
Mean age at diagnosis (years)	38	38	38	41
Sex				
Male	35	19	18	37
Female	178	66	48	85
Site of tumour				
Trunk	44	24	25	50
Head and neck	45	21	19	28
Extremities	124	40	22	44
Size of resection margin				
<2 cm	39	10	8	13
2 cm	18	17	12	24
2.1–4.9	18	7	3	10
≧5 cm	138	51	43	75
Tumour thickness				
≦0.5 mm	71	23	34	67
0.51–1.00 mm	142	62	32	55
Level of invasion				
II	111	51	52	96
III	88	31	14	24
IV A	14	3	0	1
IV B	0	0	0	1
Mitoses per mm^2				
<mm^2 tumour tissue	87	37	38	73
0	35	16	8	10
1–4	80	21	18	30
5–9	9	4	2	5
>9	0	3	0	1
unclassifiable	2	4	0	3
Ulceration				
No	210	82	63	121
Yes	3	3	3	1
Lymphocytic reaction				
Slight (0–1)	80	21	5	18
Moderate (2)	45	12	9	11
Extensive (3–4)	88	52	52	93
Predominant cell type				
Nevoid	51	15	9	26
Spindle	12	8	4	1
Epithelioid	99	49	45	79
Mixture	51	13	8	16
Total no. of patients	213	85	66	122

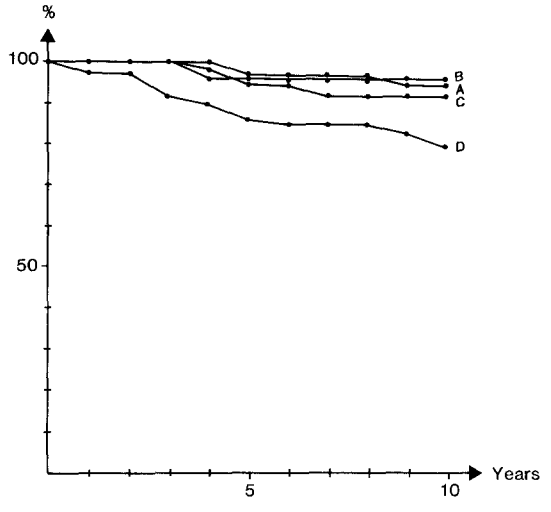

Fig. 3. Cumulative survival rates for 213 patients without regression (*A*), 85 patients with slight active regression (*B*), 66 patients with marked active regression (*C*), and 122 patients with past regression (*D*)

The association between the grading of regression and the grading of other clinico-pathological characteristics is shown in Table 2.

The frequency of past regression was significantly higher than the frequency of no regression in lesions in men versus women ($p<0.005$), in lesions on trunk versus other locations ($p<0.0005$), in lesions $\leqq 0.50$ mm thick versus lesions 0.51–1.00 mm thick ($p<0.0005$), in lesions level II versus other lesions ($p<0.0005$), in lesions with <1 mm^2 tumour tissue on the cross section of tumour versus other lesions ($p<0.001$), and in lesions with extensive lymphocytic reaction versus other lesions ($p<0.0005$) (Table 2).

In contrast past regression was without significant relationship with age of patient ($p>0.2$), size of resection margin ($p>0.4$), ulceration ($p>0.6$), and dominant type of tumour cell ($p>0.1$).

The cumulative 10 year survival was significantly poorer for patients with past regression (79%) than for patients with no regression (95%), slight active regression (96%), and marked active regression (92%) ($p=0.0001$) (Fig. 3). The difference in survival for patients with no regression and active regression was not statistically significant.

For the 122 patients with past regression the 5 year (10 year) survival was 90% (87%), 87% (73%), and 79% (77%) if the horizontal width of the fibrotic area was 0.6–2.5 mm, 2.6–4.0 mm, and >4.0 mm, respectively. The differences were not significant ($p>0.5$). (Fibrotic areas with horizontal width <0.6 mm was not recorded as past regression). For patients with vertical thickness of fibrosis <0.5 mm and $\geqq 0.5$ mm the 5 year (10 year) survival was 91% (84%) and 77% (77%), respectively. The difference was not significant ($p>0.15$).

We found no statistically significant relationship between survival and different combinations of subgroups of past regression and/or subgroups of the other clinico-pathological characteristics.

Discussion

In the present study of 486 patients with stage I melanoma ≤ 1 mm thick the frequency of melanomas with no, active, and past regression was 44%, 31% and 25%, respectively. This means that more than half of the lesions showed signs of regression histologically. This is in accordance with McGovern et al. (1983) who found active or past regression in 58% of 353 thin cutaneous melanomas. Trau et al. (1983) found active or past regression in 36% of 116 thin melanomas. The frequency of past regression was 25% in the present study. In 3 other studies the frequency varied from 15% to 31% (Gromet et al. 1978; McGovern et al. 1983; Paladugu and Yonemoto 1983). In the present study past regression was significantly more frequently seen in lesions in men, on trunk, level II, ≤ 0.5 mm thick, with extensive lymphocytic reaction, and with < 1 mm^2 tumour tissue on the cross section. These results support the finding of Trau et al. (1983), that thin melanomas with regression were particularly level II melanomas and lesions located on trunk.

The survival for patients with thin melanomas was adversely affected by the presence of past regression ($p = 0.0001$) (Fig. 3). In contrast the survival was not significantly influenced by the finding of active regression.

The greater the horizontal width and the vertical thickness of the fibrotic area, the poorer the survival for patients with sign of past regression in thin melanomas. The prognostic change, however, was not statistically significant. This may be due to the fact that the available histological sections from the lesions might demonstrate neither the maximal fibrotic width nor the maximal fibrotic thickness. Futhermore, the number of deaths in the different subgroups of past regression was rather small. The range of the fibrotic thickness was small (Table 1) due to the shrinkage of the fibrotic scar. This reduces the prognostic value of measuring the fibrotic thickness. In contrast, the range of the horizontal width of the fibrotic area was large (Table 1), and we think that this variable may be a valuable prognostic guide in thin melanomas with past regression.

The present results are in accordance with Gromet et al. (1978) and Paladugu and Yonemoto (1983) who found, that thin melanomas with regression frequently metastasized (5 out of 23 cases and 5 out of 11 cases, respectively). The suggestion of Paladugu and Yonemoto (1983), that the prognostic variables in such cases should include both the thickness of the viable tumour and the thickness of the inflammatory infiltrate has been challenged by Wolinsky and Silvers (1983).

In contrast to the present study McGovern et al. (1983) found that the 10 year survival for patients with thin melanomas was not influenced by partial regression, although the frequency of metastases was slightly higher (8%) if regression was seen, than if it was not (5%). Trau et al. (1983) and Briggs et al. (1984) did not find regression to be of prognostic importance in their studies of 116 and 90 thin melanomas, respectively.

Attempts to combine subgroups of past regression and/or subgroups of other clinico-pathological characteristics did not improve the prognostic evaluation in thin melanomas with past regression.

In conclusion, the demonstration of past regression in thin melanomas clinical stage I adversely affected survival significantly. The maximal horizontal width of the fibrotic area may be a useful prognostic factor in such lesions. The demonstration of active regression without fibrotic areas did not influence the survival significantly.

Acknowledgements. This study was supported by grants from the Danish Cancer Society (59/77), and the Danish Medical Research Council (512-20346). The authors are grateful to Dr. G. Olsen and Dr. H. Johansen for valuable support, the Statistical Research Unit, and the Danish Cancer Registry for statistical and data management assistance, and the departments of pathology of the following hospitals for providing histological material: 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 F. Centralsygehus, Roskilde Amtssygehus, Odense Sygehus, Svendborg Sygehus, Aarhus Kommunehospital, Aarhus Amtssygehus, Aalborg Sygehus, Holstebro Centralsygehus, Hjørring Sygehus, and Vejle Sygehus.

References

Breslow A (1970) Thickness, cross-sectional areas, and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 172:902–908

Breslow A (1975) Tumor thickness, level of invasion, and node dissection in stage I cutaneous melanoma. Ann Surg 182:572–575

Briggs JC, Ibrahim NMN, Hastings AG, Griffiths RW (1984) Experience of thin cutaneous melanomas (<0.76 mm and <0.85 mm thick) in a large plastic surgery unit: a 5 to 17 year follow-up. Br J Plast Surg 37:501–506

Gromet MA, Epstein WL, Blois MS (1978) The regressing thin malignant melanoma. A distinctive lesion with metastatic potential. Cancer 42:2282–2292

McGovern VJ (1975) Spontaneous regression of melanoma. Pathology 7:91–99

McGovern VJ, Shaw HM, Milton GW (1983) Prognosis in patients with thin malignant melanoma: influence of regression. Histopathology 7:673–680

Paladugu RR, Yonemoto RH (1983) Biologic behavior of thin malignant melanomas with regressive changes. Arch Surg 118:41–44

Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG (1977) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 35:1–39

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

Trau H, Rigel DS, Harris MN, Kopf AW, Friedman RJ, Gumport SL, Bart RS, Grier RN (1983) Metastases of thin melanomas. Cancer 51:553–556

Wolinsky S, Silvers DN (1983) Biologic behavior of thin malignant melanomas with regressive changes. Arch Surg 118:992

Accepted August 8, 1985