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PREOPERATIVE IRRADIATION OF MALIGNANT MELANOMA

A multifactorial statistical analysis of survival

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Abstract

This retrospective investigation concerns 212 cases of malignant melanoma from the period 1965 to 1979. Before operation 53 cases were given radiation therapy. The aim of the study was to assess whether this treatment had any influence on survival. Clinical follow-up and revision of the histologic material has been done. The tumours were classified according to CLARK et coll. (3) and divided into thickness groups (2). Statistical analysis by COX's regression model (4) indicated that survival was dependent on tumour thickness (significance level 1%) and preoperative irradiation (significance level 5%). No influence from tumour location was noted. A prospective randomized study is proposed in order to analyse the effect of preoperative irradiation.

Radiation therapy of malignant melanoma has mostly been reserved for inoperable primary tumours and metastases. In 1960 HELLRIEGEL (8) reported on radiation therapy of 342 cases of malignant melanoma from a period of 25 years. Preoperative treatment had been given in a small number of cases, which had a high 5-year survival rate. An experimental study by ROHDE & WISKEMANN (17) demonstrated that transplantation of mice melanoma failed after a high dose radiation treatment.

These reports suggested that preoperative irradiation of malignant melanoma might have a positive effect. Therefore, during the period 1965 to 1979, cases with possible malignant melanoma were given radiation therapy before operation. In an attempt to evaluate the effect, the cases have been reviewed and their survival compared with non-irradiated cases.

Material and Methods

The material consisted of 212 cases. Of these 53 were given preoperative radiation therapy. The first case in the series dates from January 1965. All cases have been followed up till May 1982.

Radiation therapy. The treatment was given 48 to 72 hours before operation with Siemens Dermopan unit at 50 kV, 25 mA, 1 mm Al filter and FSD of 15 cm. A single dose of 100 Gy was given. The margin to the tumour was at least 10 mm. The treatment created an intense erythema and at the following operation the whole erythematous area was excised.

Clinical data. Data were obtained from clinical records. Patients who had not been recently examined were summoned for follow-up. Sex and age of the patients were registered. The tumour location was subdivided into four groups: Trunk, arms, legs and other sites, the last group mainly consisting of tumours of the head. Clinical staging was as usual: Stage I no metastases, stage II regional metastases and stage III distant metastases. The operative procedures were divided into four categories: Local excision (<5 cm margin), wide excision (≥5 cm margin), local excision followed by wide excision (reexcision) and other procedures. The last group

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included patients initially treated with local excision and later reexcised with a margin less than 5 cm. In some cases it was not possible to decide the mode of operation from the operative report.

The deaths were analysed in detail to establish whether the cause of death was malignant melanoma or intercurrent disease. Autopsy was done in only 19 of 64 deaths. In the other cases the cause of death was ascertained from death certificates supplemented with clinical descriptions in records and interviews with physicians or relatives of the patients.

Histologic data. All slides were reviewed by two pathologists, without knowledge of the clinical course. There were at least six sections from each tumour. Tumour type, level of invasion according to CLARK et coll. (3) and tumour thickness (2) were registered. Ulceration, inflammation, pigmentation and mitotic activity were also noted but not used in the statistical analysis. Some tumours with an undecided epidermal component were characterized as unclassified tumours. When the two pathologists had different opinions on the melanoma type in a special case, the problem was discussed until they came to an agreement.

Statistical methods. The material was cross-tabulated in many directions with chi-square tests to check any significant relationship. COX's regression model (4) was used in a multifactorial analysis to examine each of the factors for its influence on the survival while at the same time accounting for the contribution of all other factors. The model postulates that the hazard of cancer mortality (death intensity) —λ— depends on the time and the risk factors (covariates) $z_1, \ldots, z_p$, according to the formula

$$\lambda(t, z_1, \ldots, z_p) = \lambda_0(t)e^{\beta_1 z_1 + \ldots \beta_p z_p}$$

In this formula t is time since diagnosis and $\beta_1, \ldots, \beta_p$ are regression coefficients to be estimated.

The values of the regression coefficients were estimated by maximizing the partial likelihood function proposed by COX (4). Using the asymptotic maximum likelihood theory, it is possible to construct a likelihood ratio statistic to test whether all p regression coefficients are equal to zero. Under this hypothesis the test statistic has an approximate chi-square distribution with p degrees of freedom. The maximum likelihood estimator of each β_i is approximately normally distributed. Therefore it is possible to construct confidence intervals for each β_i with standard methods.

A more detailed description of the statistical methods has been given by COX (4) and by DANIELSSON & HOLMQVIST (5). The latter have applied COX's methods on this material by developing a computer program, which produces the statistics mentioned and describes the results by means of survivor functions.

Table 1

Tumour location and sex distribution (per cent in parentheses)

Location	Females	Males	Total
Trunk	33	61	94 (44.3)
Upper extremity	14	10	24 (11.3)
Lower extremity	50	19	69 (32.6)
Other sites	19	6	25 (11.8)
Total	116 (54.7)	96 (45.3)	212 (100)

Results

The distribution of tumour location and sex corresponds to findings in other studies (7, 12). In males most melanomas were located on the trunk, in women most tumours were situated on the legs (Table 1). The tumour types occurred in expected percentage (Table 2). Most tumours were of the superficial spreading type (SSM). About 50 per cent of the very thin melanomas had been treated by local excision (Table 3). Thicker melanomas had more often been treated by wide excision. Reexcision was common in all thickness groups, obviously when melanoma was a surprise diagnosis.

Radiation therapy had been given with about the same frequency to SSM and nodular melanoma (NM). Almost half of the few unclassified melanoma (UM) but only three cases of lentigo maligna melanoma (LMM) had been irradiated (Table 4). Among the patients treated by local excision 20 per cent had been given preoperative irradiation. The corresponding figure for tumours operated with wide excision was 75 per cent. For obvious reasons only few (two) tumours treated by reexcision were irradiated. No tumour operated by other procedures was irradiated.

No histologic changes, which could be related to radiation therapy, were seen in the sections. There

Table 2

Melanoma types in relation to thickness (per cent in parentheses)

Type	Thickness (mm)				Total
	<0.76	0.76–1.50	1.51–3.99	>3.99	
Lentigo maligna melanoma (LMM)	11	7	5	3	26 (12.3)
Superficial spreading melanoma (SSM)	40	39	34	12	125 (59.0)
Nodular melanoma (NM)		4	16	25	45 (21.2)
Unclassified melanoma (UM)	3	2	7	4	16 (7.5)
Total	54 (25.5)	52 (24.5)	62 (29.2)	44 (20.8)	212 (100.0)

Table 3

Operative procedure in relation to tumour type and thickness (per cent in parentheses)

	Local excision	Wide excision	Re-excision	Other procedures	Total
Tumour type					
LMM	14	3	7	2	26 (12.3)
SSM	47	24	45	9	125 (59.0)
NM	11	14	19	1	45 (21.2)
UM	4	7	3	2	16 (7.5)
Thickness (mm)					
<0.76	28	6	14	6	54 (25.5)
0.76–1.50	16	9	23	4	52 (24.5)
1.51–3.99	19	18	21	4	62 (29.2)
>3.99	13	15	16	0	44 (20.8)
Total	76 (35.9)	48 (22.6)	74 (34.9)	14 (6.6)	212 (100.0)

Table 4

Number and percentage of preoperatively irradiated cases in relation to tumour type, thickness and operative procedure

	Preoperatively irradiated cases	
	No.	Per cent
Tumour type		
LMM	3/26	11.5
SSM	30/125	24.0
NM	13/45	28.9
UM	7/16	43.8
Thickness (mm)		
<0.76	5/54	9.3
0.76–1.50	14/52	26.9
0.51–3.99	21/62	33.9
>3.99	13/44	29.5
Operative procecure		
Local excision	15/76	19.7
Wide excision	36/48	75.0
Reexcision	2/74	2.7
Other procedures	0/14	0

was no cellular degeneration, no increase of inflammatory cells and no vascular dilatation. A small muscular necrosis beneath the irradiated area was the only registered complication.

The cause of death could not be defined in two cases. The remaining material is presented in Table 5.

Survival analysis. COX's regression model was used with factors known from earlier investigations to influence survival. We selected tumour type (3, 12) thickness (2), operative procedure and location (11) as potential prognostic factors. In these groups we first tried to estimate the relative importance of the factors (Table 6). Thickness was assumed to exert influence on survival according to the actual measure. The effect of radiation therapy was the main issue of the investigation and Table 7 shows the result of the analysis. Only thickness had a significantly positive value indicating that patients with thicker melanoma tended to have a shorter

Table 5

Number of preoperatively irradiated cases in relation to all patients in different groups

	No. of cases
All patients	53/210
Dead from MM	11/47
Dead from other causes	10/17
Clinical stage I	48/193
Dead from MM	8/34
Dead from other causes	9/16
Observed ≥ 3 years	26/115
Dead from MM	2/11
Dead from other causes	6/12

Table 6

Subjectively estimated importance of factors

Tumour type		Operative procedures		Location	
LMM	1	Reexcision	1	Other locations	1
SSM	2	Wide excision	1.5	Upper extremity	2
UM	2.5	Other procedures	3	Lower extremity	3
NM	4	Local excision	4	Trunk	4

Table 7

Results of statistical analysis according to Cox (4). Subjective model

Covariate	Estimated parameter	Confidence interval
Irradiation	−0.2095	−1.2957–0.8767
Tumour type	0.3097	−0.2157–0.8352
Operative procedure	−0.1339	−0.4982–0.2304
Location	−0.0029	−0.4609–0.4551
Thickness	0.0025	0.0008–0.0043

χ^2-value with 5 degrees of freedom = 58.30.

Table 8

Factors in objective analysis

$z_1 = \begin{cases} 1 & \text{irradiated} \\ 0 & \text{not irradiated} \end{cases}$

$z_2 = \begin{cases} 1 & \text{tumour type SSM} \\ 0 & \text{not tumour type SSM} \end{cases}$

$z_3 = \begin{cases} 1 & \text{tumour type UM} \\ 0 & \text{not tumour type UM} \end{cases}$

$z_4 = \begin{cases} 1 & \text{tumour type NM} \\ 0 & \text{not tumour type NM} \end{cases}$

z_5 = 1–999 (thickness)

$z_6 = \begin{cases} 1 & \text{wide excision} \\ 0 & \text{no wide excision} \end{cases}$

$z_7 = \begin{cases} 1 & \text{other procedure} \\ 0 & \text{no other procedure} \end{cases}$

$z_8 = \begin{cases} 1 & \text{local excision} \\ 0 & \text{no local excision} \end{cases}$

$z_9 = \begin{cases} 1 & \text{upper extremity} \\ 0 & \text{not upper extremity} \end{cases}$

$z_{10} = \begin{cases} 1 & \text{lower extremity} \\ 0 & \text{not lower extremity} \end{cases}$

$z_{11} = \begin{cases} 1 & \text{trunk} \\ 0 & \text{not trunk} \end{cases}$

survival. To avoid the uncertainty in a subjective estimation we made a similar analysis where the importance of all different factors was analysed separately (Table 8). Also the new analysis showed a dependence of survival on thickness (Table 9). The parameter for radiation therapy was negative at the significance level 5%, which meant that preoperative irradiation may have had a positive influence.

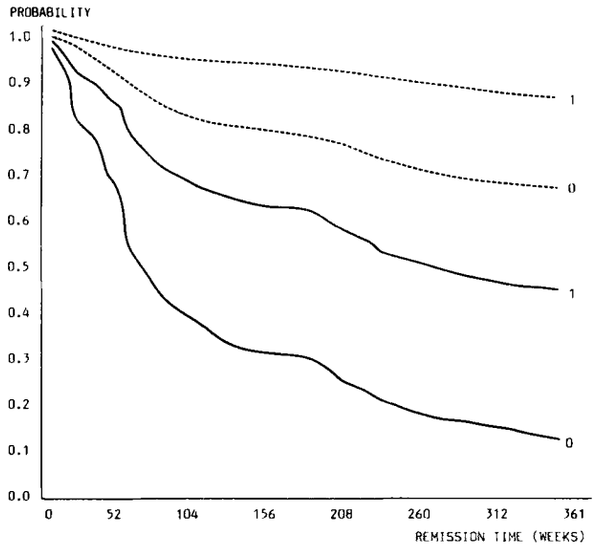
If one excluded the factors 'location' from the analysis there were no significant changes in the estimated parameters β. This indicates that location was unimportant. On the other hand there was a considerable change in the results when factors for the type of operation were excluded. Thus the type of operation seemed to have had influence, directly or indirectly, on survival.

A corresponding analysis was done on the two treatment groups, local and wide excision, which included all irradiated cases except two. This analysis gave almost the same results as the more extensive one, indicating that the method is sensitive to disturbing factors. The results of the statistical analysis can be illustrated by empirical survivor function curves (Figure).

Discussion

In vitro tests on the radiosensitivity of human melanoma cells indicate a large ability to repair a sublethal radiation damage (1, 9). This fact has led to attempts to treat metastases and recurrences with high individual doses. OVERGAARD (15) reported on a series of 49 cases treated with varying doses. He found correlation between response and dose per fraction but not between response and total dose. STRAUSS et coll. (19) obtained the same results in a clinical trial with individual doses of ≥6 Gy compared with doses of 2 to 5 Gy. HORNSEY (10) made a retrospective analysis of 52 patients from three different treatment centres. The result seemed to indicate that fractions of 4 to 8 Gy were more effective than fractions of 2 to 3 Gy.

Thus a high fraction dose is nothing new. In spite of the fact that our dose was extremely high (100 Gy) there was only one case of local necrosis. A



COX's model. Empirical survival function. Parameters: 1 = radiation therapy given, 0 = no radiation therapy given. Covariates: Upper curves = NM, reexcision, thickness 0.5 mm, lower curves = NM, reexcision, thickness 7.0 mm.

Table 9

Results of statistical analysis according to COX (4). Objective model

Covariate	Estimated parameter	Confidence interval
z_1	−0.9393	−2.5468–0.6683
z_2	−1.0574	−2.9173–0.8024
z_3	0.1432	−1.7867–2.0731
z_4	0.4794	−1.6214–2.5801
z_5	0.0023	0.0004–0.0042
z_6	−0.2192	−1.3838–0.9454
z_7	0.6919	−0.8795–2.2633
z_8	−0.7735	−3.9934–2.4465
z_9	0.9986	−1.0463–3.0435
z_{10}	1.7363	−0.5568–4.0295
z_{11}	1.2318	−0.8790–3.3426

χ^2-value with 11 degrees of freedom = 75.77. Upper 95% confidence interval for β_1 is $\beta_1 \leq -0.0835$.

small amount of soft tissues and, in some cases, bone under the excised specimen received a radiation dose of >30 Gy. There are reports of development of soft tissue sarcomas and osteogenic sarcomas after radiation treatment of retinoblastomas and other tumours (6, 13). Our patients are therefore continuously observed.

Preoperative irradiation of malignant melanoma has been evaluated in some previous reports. The series of HELLRIEGEL (8) included seven cases which had been given preoperative treatment, six survived five years. POPPE (16) gave pre- and postoperative treatment in 47 cases in stage I, 33 of which (70%) survived five years. MIESCHER (14) treated 53 cases in stage I preoperatively of which 64 per cent survived five years without any symptoms of melanoma disease. STORCK et coll. (18) reported on 88 cases in stage I treated in the same way with about 30 Gy in one dose or divided into several smaller doses. Of these 53 (60%) survived five years. The survival was higher (78%) in a series given postoperative treatment. These authors tried to evaluate the 'malignancy' of the compared groups and concluded that it was about the same in the two groups.

The treatment series mentioned do not show any significant influence of preoperative irradiation of malignant melanoma. In the present investigation there was statistical indication that the radiation treatment may have had a positive effect on survival. A prospective randomized study ought to be of interest.

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