Life expectancy after irradiation of melanoma eyes prior to enucleation

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Abstract

In July 1980, a prospective study was undertaken to evaluate irradiation of melanoma eyes prior to enucleation. The criteria for inclusion were: a melanoma too large for plaquing and the absence of detectable metastases. Vertical stationary electron beam irradiation (10-12 MeV) was applied to the melanoma eye and orbit in increasing doses from 12-50 Gy following satisfactory wound healing. Between July 1980 and July 1986 preoperative irradiation was carried out on 26 melanoma eyes. The average diameter of the tumor base was 15 mm, the height 10 mm. Enucleation was performed with minimum touch to the eye. The cytology of the melanomas was 17 spindle, five mixed, three epithelioid, and one necrotic cell type. After an average follow-up of three years (ten to 82 months), five of 26 patients (19%) had died due to metastases and one was alive with metastases. After four and a half years (25-100 months), nine of 26 patients (35%) had died due to metastases and one was alive with metastases. After an average follow-up of five years (37-109 months), 12 of 26 patients (46%) had died due to metastases, one was alive with metastases, and another had a second primary malignancy (carcinoma of the lip). All three patients with melanoma of the epithelioid cell type had died during the second postoperative year. The results of this small series suggest that pre-irradiation of a melanoma eye has no beneficial effect on a patient's life expectancy, but more likely an adverse effect. Due to the high mortality rate despite pre-enucleation irradiation, the therapy was abandoned and instead a special minimum-touch technique, the so-called hypertensive gas-"no touch" technique for enucleation introduced previously, has been utilized since May 1987.

Introduction

The thesis of Zimmerman and his associates[1], supported by a retrospective study of 2652 patients with choroidal melanoma, reported that the risk of metastases after enucleation was highest during the second year after enucleation (approximately 8%). This was attributed to manipulation of the globe during enucleation causing seeding of viable tumor cells. With this in mind and to avert the seeding of tumor cells, we began irradiation of the globe and orbit of melanoma eyes prior to enucleation. We report here the results of a prospective study carried out at the University of Tübingen Eye Clinic from July 1980 to August 1989.

Material and methods

The study consisted of 26 patients with choroidal melanoma. Criteria for inclusion were: *1.* a choroidal melanoma too large for treatment with a radioactive plaque; and *2.* the absence of detectable metastases, as determined by an extensive tumor search, including testing by SGOT, SGPT, GTT, X-ray of the lungs, sonography and computer tomography (CT) of the abdomen, and CT scan of the brain and orbit. There were 15 males and 11 females. The age of the patients ranged from 25 to 75 years; the average age was 58.5 years.

The localization of the choroidal melanoma was posterior to the equator in 15 (58%) eyes and anterior in 11 (42%). The average base diameter of the tumors was 15 mm (range: 10-20 mm), and the height 10 mm (range: 6-14 mm). There was one additional tumor with a base diameter of 9 mm and a height of 4 mm which was enucleated because an extrascleral extension

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was suspected.

Vertical stationary electron beam irradiation with an energy of 10-12 MeV was applied to the melanoma-containing eye and orbit in increasing doses. Depending on satisfactory wound healing, the following doses were applied: 12 Gy in two patients from July 1980 to March 1982, 16-20 Gy in five patients from April 1982 to February 1983, and thereafter 30-40 Gy in 18 patients and 50 Gy in one patient (manifest extrascleral extension of melanoma) from March 1983 to July 1986.

Enucleation was performed in ten patients during the first week after irradiation and in 16 patients during the second to fifth week. The latter group had received 30-50 Gy; the extensive orbital edema had made an earlier enucleation too difficult.

The enucleation was performed with a minimum trauma to the eye in order to prevent changes in intraocular pressure. The eye muscles were resected with a cautery knife to avoid bleeding, and the vortex veins were cauterized before being severed. After a three-minute compression of the optic nerve with a hemostat, it was cut with the built-in blade. No implants were inserted in the orbits.

Results

In five eyes the melanoma had a collar-button contour, in 12 the tumor had perforated Bruch's membrane to some degree, and scleral perforation was present in three eyes. The cytology of the melanomas was as follows: spindle cells in 17 eyes, mixed in five, epithelioid in three, and necrotic in one.

At the first follow-up visit in May 1987, five patients or 19% (five of 26), had died of metastases. Follow-up ranged from ten to 82 months with an average of 34 months. The average interval between enucleation and death was 30 months. Three of the five patients had died during the second postoperative year, one patient had died of a heart attack with no clinical evidence of metastases, and one patient was alive with metastases (Fig. 1).

Of the 20 patients alive, 19 had returned for the follow-up examination. Their conjunctival sockets had healed satisfactorily. With the prosthesis in place, there was an apparent "enophthalmus" in all but one patient. The enophthalmus measured between 1 and 5 mm. Two patients had difficulty with the fitting of their prosthesis, and an implant was inserted in a secondary procedure in one patient.

At the second follow-up visit, between August and November 1988, nine patients or 35% (nine of 26) had died of metastases. Follow-up ranged from 25 to 100 months with an average of 53 months. The average time elapsing between enucleation and death was 26 months. Six of the nine patients (66%) had died during the second postoperative year. One patient was alive with metastases.

Fig. 1. A 63-year-old patient with a small melanoma metastasis on the contralateral lid ten months after enucleation of a pre-irradiated (30 Gy) melanoma. The lid tumor was resected (mixed cell type as primary tumor). The patient died 25 months after enucleation due to liver metastases, respectively 15 months after detection and resection of the lid metastasis.

At the third and final follow-up visit in August 1989, 12 patients or 46% (12 of 26) had died of metastases. Follow-up ranged from 37 to 109 months with an average of 59 months. The average time elapsing between enucleation and death was 36 months. Six (50%) of the 12 patients had died during the second postoperative year, three at three years, and one each at five, six and seven years (Table 1). In 11 patients, no metastases or secondary primary malignancies could be detected in an extensive tumor search; one was alive with metastases and another had an additional malignancy, a small lip carcinoma (patient is a heavy pipe smoker) (Table 2). The lip carcinoma, found five and a half years after enucleation of the melanoma eye, was resected. The histological section showed a squamous cell carcinoma (Fig. 2).

Table 1. Dosage of irradiation, cytology and time elapsing between enucleation and death (n=12) due to melanoma metastases

Dose of irradiation (Gy)	*Cytology*	*Death after enucleation*	
		Months	*Years*
20	Epithelioid	20	
30	Spindle	17	
30	Mixed	18	
30	Epithelioid	18	>1-2
30	Mixed	24	
40	Epithelioid	21	
20	Spindle	35	
30	Spindle	34	>2-3
40	Necrotic	30	
20	Spindle	55	5
40	Mixed	74	6
12	Spindle	87	7
	Average	36.1	

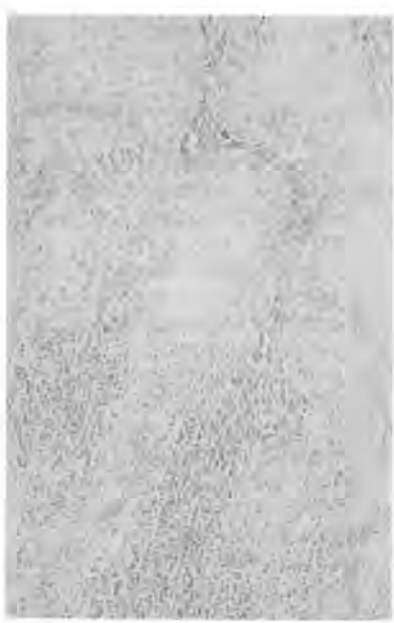

Fig. 2. Histological section of a squamous cell carcinoma of the lip, a secondary primary malignancy developed 5.5 years after enucleation of a pre-irradiated choroidal melanoma in a 69-year-old patient. Note the atypical epithelial basement membrane and the invasion of the dermis. There is a moderate to strong lymphocytic reaction. The surface epithelium is visible at the top (toluidine blue, ×80).

Table 2. Deaths from metastases after enucleation of 26 pre-irradiated melanoma eyes

Follow-up	*Alive*			*Death due to*	
	No metastases No additional malignancy	*With metastases*	*With additional malignancy*	*Metastases*	*Heart attack*
May 1987					
10-82 months (average 3 years)	19	1	–	5 (19%)	1
August-November 1988					
25-100 months (average 4.5 years)	15	1	–	9 (35%)	1
August 1989					
37-109 months (average 5 years)	11	1	1	12 (46%)	1

Discussion

Reports on clinical results after irradiation of a choroidal melanoma prior to enucleation are sparse and, in these, the number of patients ranges from 11 to 80. The first data were published by Rousseau *et al.*[2], followed by Char and Phillips[3], Augsburger *et al.*[4], Kreissig and Rohrbach[5], Kenneally *et al.*[6], Char *et al.*[7], Kreissig *et al.*[8] and Bornfeld *et al.*[9]. These data seem to indicate that there might be no beneficial, and possibly even an adverse, effect from irradiation on a patient's life expectancy.

Our results are similar to those of Char and Phillips[3] when applying similar periods of follow-up. For our data, analyzed at an average follow-up of 37 months, the death rate was 19% (five of 26) *versus* 14% (four of 28) for their series with an average follow-up of 24 months. Considering our results with an average follow-up of 53 months, the death rate from metastases had increased to 35% (nine of 26) *versus* 29% (12 of 41) in their series[7] with an average follow-up of 47 months. This already suggests that there might be no beneficial effect from pre-irradiation on a patient's life expectancy.

A recent review of our data with an even longer average follow-up of five years (59 months) indicates that the mortality rate has increased to 46% (12 of 26). This further supports the concept that irradiation prior to enucleation does not seem to decrease tumor-related mortality, but rather has an adverse effect on it. This is more evident in our series, since we had administered a larger dose of pre-irradiation: in 19 of 26 patients (76%), the dose ranged from 30 to 50 Gy.

The concept that a larger dose of irradiation might not decrease, but rather increase, the mortality rate could also explain the somewhat better results of Bornfeld *et al.*[9]. In contrast to us, they administered a much smaller dose of irradiation, ranging between 8.5 and 20 Gy. They observed a lower death rate of between 18 and 22% during an average follow-up of five years, compared to our mortality rate of 46% during the same period of time.

These observations would even fit in with the concept of Jager *et al.*[10], who suggested that radiotherapy of a melanoma may "decrease the expression of HLA class II antigens on the tumor and therefore lower the immunologic recognition". However, the most likely explanation for the high mortality rate despite pre-irradiation is the presence of pre-existing and heretofore undetectable micrometastases. Perhaps further investigation with monoclonal antibodies will provide more sensitive tests for earlier detection[11].

In our series, death from metastases occurred in all three melanoma patients with epithelioid cells, and they died as early as during the second postoperative year. This is in agreement with a report by McLean *et al.*[12]. The remaining nine patients had various cell types and death occurred later, between the second and seventh year after enucleation (Table 1).

We discontinued pre-enucleation radiotherapy for our melanoma patients in May 1987. By that time, we had obtained the discouraging results of our first re-examination, implying a death rate of 19% during an average follow-up of three years, despite pre-irradiation. The death rate at that time rose to 29% when including patients with only a two-year follow-up.

Our decision to abandon pre-irradiation was not only reinforced by the findings of low life

Fig. 3. A 27-year-old patient: the right eye and orbit were irradiated (30 Gy) prior to enucleation of a choroidal melanoma (base diameter 20 mm, height 12 mm). With the prosthesis in place, there is an enophthalmus of 5 mm.

expectancy, but also by the psychological stress observed in all patients due to the numerous irradiation sessions and the postponement of enucleation while presumed prophylaxis was administered, and also by the postoperative cosmetic defects which occurred (Fig. 3). In this small series, it became apparent that the atrophy of pre-irradiated orbital tissues was more extensive. This finding has been examined by us in a comparable series of eyes without prior irradiation. However, the question has arisen as to why an implant was not inserted. Our reservations in this respect were due to the primary uncertainties concerning subsequent satisfactory wound healing and not so much due to the risk of orbital metastases being a rare finding.

Only a positive conclusion from the Collaborative Ocular Melanoma Study[13] could reverse our present reservations towards pre-enucleation irradiation. As an alternative, we are now utilizing a special minimum-touch technique during enucleation. This is the so-called ocular hypertensive gas technique, a kind of gas-"no-touch" technique for enucleation[14,15]. This technique does not require additional instruments nor does it prolong surgery, and it can prevent changes in intraocular pressure due to the presence of a rock-hard globe during the period of enucleation. Additionally, removal of the rock-hard eye is faster with practically no bleeding from the globe.

Concerning the frequency of another primary malignancy, to date a small lip carcinoma was detected in one of our 26 patients (4%) at one of the routine examinations. The carcinoma had developed during the sixth year after enucleation of a melanoma eye. Naumann[16] described the frequency of secondary primary malignancies as being 4 to 6%. Seddon *et al.*[17] as 8.6% and Gliem *et al.*[18] as 10%. This further supports the need for a meticulous follow-up of melanoma patients at yearly intervals, including an extensive search for metastases and also for secondary primary malignancies, since early treatment may still be possible.

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