

delay in metastases nor an increase in the patient's postoperative life expectancy.

The results in a series reported by Char and Phillips⁶ are somewhat comparable to ours when applying similar periods of follow-up. If our data are analyzed at an earlier average follow-up of 37 months, the death rate is 19.3% (5 of 26) for our series versus 14% (4 of 28) for their series with a 24-month average follow-up. The combined data of these two series reinforce the opinion that irradiation of the eye and orbit before enucleation of a melanoma is of little value. When considering the results of our last and herein reported reexamination with a mean follow-up of 53 months, the rate of death from metastases has increased to 34.6% (9 of 26), and one patient was living with metastases. This furthermore suggests that undetected micrometastases might have existed prior to irradiation. In addition, it would fit into the concept of Manschot and van Strik⁷ who suggested that a positive effect of PERT on the rate of metastasis could become evident not earlier than 10 years after enucleation. Manschot and van Peperzeel⁸ explained this long postoperative interval by the low growth rate of seeded metastases.

Augsburger et al⁹ showed in histologic studies that mitotic activity of melanoma cells was reduced in patients who had PERT compared with a control group that did not. However, they concluded that it "does not necessarily imply a reduction of the incidence or growth of metastatic foci." Rousseau et al¹⁰ demonstrated in an animal model—and Kenneally et al¹¹ in patients—that pre-enucleation irradiation altered the subsequent *in vitro* growth of melanoma cells. Jager et al¹² suggested that although radiotherapy of a melanoma may interfere with the division of the cells in the tumor, it may also "decrease the expression of HLA class II antigens on the tumor and therefore lower the immunologic recognition."

These controversial findings and interpretations of PERT by others have already cast doubt on its therapeutic value. Our own survival results provide additional clinical evidence that PERT does not improve the patient's life expectancy. Our decision to discontinue pre-enucleation radiotherapy for melanoma patients was reinforced by the observation of sustained stress that many of the patients displayed during the

postponement of enucleation caused by the numerous irradiation sessions. Only a positive conclusion about PERT from the growing data of the North American Collaborative Ocular Melanoma Study^{13,14} could influence us to reverse our present position.

Key words: choroidal melanoma, enucleation, irradiation, metastases, preoperative external beam radiation therapy (PERT), life expectancy.

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IRRADIATION OF CHOROIDAL MELANOMAS BEFORE ENUCLEATION?

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Abstract: The eyes of 26 patients with choroidal melanomas were irradiated before enucleation at the University Eye Clinic in Tübingen. Preoperative external beam radiation therapy (PERT) was administered between July 1980 and July 1986. Follow-up ranged from 25 months to 8 years, 4 months with a mean follow-up of 53 months. The average diameter of the tumor base was 15 mm and the height 10 mm. Before enucleation vertical stationary electron beam irradiation (10-12 meV) was applied to the tumor-containing eye and the orbit. The dose was increased during the course of the study from 12 to 40 Gy. Enucleation was performed by a technique that cauterized the

vasculature before severing it and avoided maneuvers that would cause changes in intraocular pressure. The patients were reexamined between August and November 1988. Nine (34.6%) had died of metastases of melanoma, six of them during the second postoperative year; one patient was alive with metastases. Subsequent death occurred in all patients who had melanomas of epithelioid cell type (3 of 3) and in no patients who had melanomas of spindle A cell type (0 of 3). In this small series PERT had no apparent beneficial effect on the patient's life expectancy.

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Whether life expectancy is jeopardized by enucleation of an eye with a malignant melanoma remains a question. A retrospective study by Zimmerman, McLean, and Foster¹ indicated that the rate of metastasis after enucleation was highest (8%) in the second year after enucleation. This was attributed to the manipulation of the globe during enucleation, which caused seeding of tumor cells.

To avert seeding of viable tumor cells two approaches could be considered: apply a minimum-touch technique during enucleation, eg, the technique described by Fraunfelder et al,² or devitalize the tumor cells with irradiation before enucleation. We report our results of preoperative external beam radiation therapy

(PERT) to the globe and orbit of eyes with choroidal melanoma before enucleation.

Materials and Methods

The criteria for inclusion of patients in the prospective study were the presence of a choroidal melanoma with a base diameter larger than 14 mm or a tumor that invaded the ciliary body and the absence of detectable metastases. From July 1980 to July 1986 PERT was performed on the eyes of 26 patients with choroidal melanoma before enucleation at the University Eye Clinic in Tübingen. There were 15 men and 11 women. The age of the patients ranged from 25 to 75 years (mean age, 59 years). Seventeen patients were emmetropic and nine were hyperopic. None were myopic.

The diagnosis of melanoma was determined by binocular indirect ophthalmoscopy, biomicroscopy with the Goldmann contact lens, fluorescein angiography, transillumination, and ultrasonography using

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standardized A-scan (Kretz 7200 MA; evaluating 1 μ sec by 0.8 mm) and B-scan (Ocuscan 400).

Before irradiation all of the patients were examined for metastases. Included in the examination were transaminase values (SGOT, SGPT, GGT), chest x-ray and abdominal ultrasound findings, and computerized tomography (CT) of the abdomen when ultrasound findings suggested metastases. CT scan of the brain was also done to detect metastases and of the orbit to detect scleral perforation. In all of the 26 patients no metastases were detected before treatment.

Fifteen patients had eye symptoms for 1 to 4 months, seven patients for 5 to 7 months, one patient for 11 months, and one patient for 32 months. In two patients the tumor was found on routine examination and its duration was unknown. The localization of the choroidal melanoma was posterior to the equator in 15 eyes and anterior to the equator in 11 eyes. The mean base diameter of the tumors was 15 mm (ranging from 10 to 20 mm) and the height 10 mm (ranging from 6 to 14 mm). One additional tumor with a base diameter of 9 mm and a height of 4 mm was enucleated because extrascleral extension was suspected. An exudative detachment was present in 23 eyes. There was secondary glaucoma in three eyes.

PERT was performed in the radiology department of the University of Tübingen. In the eye with choroidal melanoma the globe and orbit were irradiated by vertical stationary electron beam irradiation with an energy of 10 to 12 MeV. From July 1980 to March 1982 a total dose of 12 Gy was applied in equal fractions on three consecutive days. After satisfactory wound healing the amount of PERT was increased. From April 1982 to February 1983 the pre-enucleation dose of 16 to 20 Gy was applied. From March 1983 to July 1986 wound healing was still satisfactory, so PERT was increased to 30 Gy. In the event of suspected extrascleral extension 40 Gy were applied; in one patient with manifest extrascleral extension, 50 Gy were given in fractions of 3 to 4 Gy per session (Table 1).

Enucleation was performed in five patients the day the last PERT was given, in seven during the first week, in five during the second week, and in nine patients during the third and fourth week. The latter two groups had received 30 to 50 Gy and had orbital edema that would have made earlier enucleation difficult.

Enucleation was performed under retrobulbar anesthesia supplemented with 2.5 ml Privin® (CIBA, Wehr, Germany) 1:1000 solution. The enucleation technique was designed to minimize surgical trauma and to prevent changes in intraocular pressure. The eye muscles were resected with a cautery knife to prevent

Table 1. Dose of PERT Before Enucleation of Choroidal Melanomas and Deaths from Metastases

Time of PERT Application	Dose (Gy)	Choroidal Melanomas (n = 26)	Deaths from Metastases (n = 9)
July 1980–March 1982	12	2	–
April 1982–February 1983	16	1	–
March 1983–July 1986	20	4	3
	30	14	4
	40	4	2
	50	1	–

bleeding. The vortex veins were localized and cauterized before they were severed. The optic nerve was cut with a hemostatic knife. Implants were not inserted in any of the orbits, because of uncertainty about the healing of irradiated tissue.

Patient follow-up lasted from 25 months to 8 years, 4 months (mean follow-up, 53 months).

Results

Upon sectioning of the enucleated eyes, five melanomas were found to have a collar button contour. There was 1+ pigmentation in six melanomas, 2+ in five, and 3+ in three melanomas (Table 2). In 12 eyes the tumor had perforated Bruch's membrane, and in three eyes there was a scleral perforation with extrascleral tumor growth.

The tumor cell type was spindle A in three melanomas, spindle B in 14, mixed in five, epithelioid in three, and necrotic in one.

By the time of the last examination, August to November 1988, nine patients had died of metastases

Table 2. Characteristics of Choroidal Melanomas After PERT and Deaths from Metastases

Characteristics	Choroidal Melanomas (n = 26)	Deaths from Metastases (n = 9)
Pigmentation		
1 (+)	12	5
1 +	6	1
2 +	5	2
3 +	3	1
Scleral perforation	3	2
No scleral perforation	23	7
Cytology		
Spindle A	3	–
Spindle B	14	3
Mixed	5	2
Epithelioid	3	3
Necrotic	1	1

Table 3. Medical Status of Patients Before and After PERT and Enucleation of Choroidal Melanoma

Medical Status	N = 26
Preoperative: no detected metastases	26
Postoperative: mean follow-up 53 months	
Deaths from metastases	9
Death from heart attack	1
Alive with metastases	1
No detected metastases	15

from their eye tumors. The mean elapsed time between enucleation and death was 26 months. Six of the nine patients died during the second postoperative year. One additional patient died of a heart attack; at the time of death there was no clinical evidence of metastases. One patient was alive with metastases. Of the 16 patients still alive, one had not returned for follow-up; he was reported to be asymptomatic (Table 3).

Of the 15 patients who returned for follow-up examination, the conjunctival sockets were found to have healed satisfactorily. With the prosthesis in place there was an apparent enophthalmus in all patients. It measured between 1 and 2 mm in four eyes, 3 and 4 mm in nine eyes, and 5 mm in two eyes (Table 4). Two patients had difficulties with the fitting of their prosthesis and an implant was inserted in a secondary procedure in one patient.

Tear production was evaluated by the Schirmer test. In four patients the irradiated side had reduced tear production. None of the patients complained of epiphora. None lost eyelashes or eyebrows.

Discussion

Despite irradiation to the globe and orbit of eyes with choroidal melanomas before enucleation, the mortality rate from metastases was 34.6% (9 of 26) after an average follow-up of nearly 4½ years (53 months). Of these, six died in the second year after enucleation, two in the third year, and one in the fifth year (Table 5).

A comparison of the results of this series with those of Zimmerman, McLean, and Foster¹ shows that the mortality rate in our patients was also highest in the second year after enucleation and this despite PERT. Admittedly, our series contained higher-risk patients; with the exception of one, all had choroidal melanomas with a mean base diameter of 15 mm and a height of 10 mm. In this context, it should be noted that none of the 26 melanoma eyes was myopic, a finding which might need further study.

In our series the deaths from metastases did not appear to correlate with the time of enucleation elapsed

Table 4. Ophthalmologic Findings in 15 Patients After PERT and Enucleation of Choroidal Melanoma

Ophthalmologic Findings	N = 15
Enophthalmus	
1–2 mm	4
3–4 mm	9
5 mm	2
Conjunctiva	
Harmless, not shrunken	15
Superior and inferior fornix present	15
Recurrence of local tumor	–

after PERT (0 to 30 days). However, age was a factor in the life expectancy of these melanoma patients. Whereas the mean age was 59 years for the entire series, it was 68.5 in the nine patients who died, and exceeded the primary mean age by 10 to 18 years in five of the nine patients who died. This is in agreement with the observation by Zimmerman and McLean,³ who found in untreated, ie, not preirradiated, uveal melanomas that the prognosis was also worse for the older patients. With regard to localization of the tumor, death from metastases occurred in only 3 (27%) of 11 anterior melanomas versus 6 (40%) of 15 posteriorly located melanomas.

As reported by McLean et al,^{4,5} deaths from metastases occurred most in the epithelioid cell type (3 of 3), less often in the mixed cell type (2 of 5), and were lower in the spindle B cell type (3 of 14). None occurred in the three patients who had melanomas of spindle A cell type (Table 2). The dose of PERT varied from 20 to 50 Gy. In this context it might be of interest that two of the three patients who died the latest (in the third and fifth year) received a lower dose (20 Gy) of PERT (Table 5). These data could suggest that the amount of PERT does not imply a

Table 5. Deaths from Metastases After Enucleation of Preirradiated Choroidal Melanoma (9 of 26 Patients)

Age at Death (Years)	Time of Death After Enucleation		Dose of PERT (Gy)
	Months	Years	
77	17		30
65	18		30
69	18		30
70	20	2	20
54	21		40
64	24		30
77	30	3	40
74	35		20
67	55	5	20
Mean: 68.5	26.4		