

MALIGNANT MELANOMAS OF THE CHOROID AND CILIARY BODY: A CLINICOPATHOLOGIC STUDY

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A SURVEY HAS BEEN MADE OF ENUCLEATED EYES submitted to the Pathology Department of Kresge Eye Institute which demonstrated upon histologic examination a malignant melanoma of the choroid or ciliary body. This group is comprised of those melanomas which were clinically diagnosed or suspected, and those which were unsuspected at the time of enucleation. An additional survey has been made of eyes received with a clinical diagnosis of malignant melanoma of the choroid or ciliary body which upon histologic examination were found not to harbor a malignant tumor.

MALIGNANT MELANOMAS OF THE CHOROID AND CILIARY BODY

Our laboratory has received 406 eyes having a malignant melanoma of the posterior segment. They occurred in 244 males and 162 females. In 335 cases, the age was recorded at the time of enucleation (Table 1). The average age was 58½, the youngest eight, and the oldest 85. All tumors were removed from Caucasians.

TABLE 1. MALIGNANT MELANOMA OF THE CHOROID AND CILIARY BODY AGE DISTRIBUTION, 335 RECORDED CASES

<i>Age</i>	<i>Number of cases</i>	<i>Per cent</i>
1-9	1	.3
10-19	2	.6
20-29	6	1.8
30-39	24	7.1
40-49	68	20.3
50-59	76	22.7
60-69	93	27.8
70-79	48	14.3
80-89	17	5.1
TOTAL	335	100.0

TABLE 2. HISTOLOGIC TYPES OF MALIGNANT MELANOMA, 406 CASES

<i>Cell type</i>	<i>Number of cases</i>	<i>Per cent</i>
Spindle A	12	3.0
Spindle B	178	43.8
Fascicular	12	3.0
Necrotic	5	1.2
Mixed	183	45.0
Epithelioid	16	4.0
TOTAL	406	100.0

TABLE 3. MALIGNANT MELANOMA OF THE CHOROID AND CILIARY BODY, 406 CASES

Malignant melanoma of the choroid		
limited to choroid	108 cases	
intraocular extensions	232 cases	340 cases
extraocular extensions	29 cases	
metastasis	51 cases	
Malignant melanoma of the ciliary body		
limited to ciliary body	10 cases	
intraocular extensions	56 cases	66 cases
extraocular extensions	12 cases	
metastasis	15 cases	

The histologic cell types found in these tumors are classified in Table 2. The tumors arose in the choroid in 340 or 83.7 per cent, and in the ciliary body in 66 or 16.3 per cent of the cases. Of the 340 cases arising in the choroid (Table 3), 108 were limited to the choroid, 232 had various intraocular extensions (Table 4), 29 showed extraocular extensions, and there was metastasis in 51. Of the 66 cases arising in the ciliary body (Table 3), 10 were limited to the ciliary body, 56 had intraocular extensions (Table 4), 12 showed extraocular extensions, and there was metastasis in 15.

It has been possible to follow 166 of these cases for five years or longer. Of these, 61 are living and well, 39 have died of unrelated causes, 66 have died of tumor metastasis of which 60 or 36.1 per cent died within five years (Table 5).

CLINICALLY DIAGNOSED MALIGNANT MELANOMA OF THE CHOROID AND CILIARY BODY

In 338 of the 406 cases of malignant melanoma of the choroid and ciliary body, the tumor was clinically diagnosed or suspected. These

TABLE 4. MALIGNANT MELANOMA OF THE CHOROID AND CILIARY BODY, INTRAOCULAR EXTENSIONS, 288 CASES

Primary in choroid, 232 cases	invades retina	136 cases
	invades sclera	115 cases
	invades optic papilla	53 cases
	invades ciliary body	40 cases
	invades iris	1 case
	invades angle meshwork	1 case
Primary in ciliary body, 56 cases	invades choroid	35 cases
	invades sclera	13 cases
	invades iris	33 cases
	invades retina	9 cases
	invades anterior chamber	2 cases
	invades angle meshwork	5 cases

TABLE 5. MALIGNANT MELANOMA OF THE CHOROID AND CILIARY BODY, DEATH FROM METASTASIS, 66 CASES

<i>Years</i>	<i>Number of cases</i>	<i>Per cent</i>
0-1	21	31.8
1-2	19	28.8
2-3	12	18.2
3-4	6	9.1
4-5	2	3.0
5-6	4	6.1
6-7	1	1.5
7-8	1	1.5
TOTAL	66	100.0

TABLE 6. CLINICALLY DIAGNOSED OR SUSPECTED MALIGNANT MELANOMA POSTERIOR SEGMENT, AGE DISTRIBUTION, 271 CASES

<i>Age</i>	<i>Number of cases</i>	<i>Per cent</i>
1-9	1	.4
10-19	2	.7
20-29	6	2.2
30-39	21	7.7
40-49	59	21.8
50-59	63	23.2
60-69	75	27.7
70-79	33	12.2
80-89	11	4.1
TOTAL	271	100.0

tumors occurred in 206 males and 132 females. The age at the time of enucleation was reported in 271 cases, the average being 55½, the youngest eight, and the oldest 82 (Table 6).

Included in our group of clinically diagnosed tumors were three prepubertal malignant melanomas of the posterior segment. The first arose in the choroid of an eight-year-old white girl, and was of the epithelioid cell type, measuring 15 mm. by 10 mm. The second arose in the ciliary body of a 10-year-old white boy, and was of the spindle B cell type, measuring 10 mm. by 6 mm. The third arose in the choroid of a 12-year-old white boy, and was of the spindle B cell type, measuring 11.5 mm. by 5.5 mm.

Of the 338 diagnosed malignant melanomas of the posterior segment, 279 or 82.5 per cent arose in the choroid, and 59 or 17.5 per cent arose in the ciliary body. There was external extension of the tumor in 29 or 8.6 per cent. In 10 cases of malignant melanoma of the choroid, P32 studies were reported as positive in seven, as negative in one, and as inconclusive in two. One hundred and twenty-five of these cases were followed for five years or longer. Of these, 45 are living and well, 23 have died of unrelated causes, 57 have died of tumor metastasis of which 52 or 41.6 per cent died within five years (Table 7). In 10 eyes there had been one or more operations for retinal detachment.

TABLE 7. CLINICALLY DIAGNOSED OR SUSPECTED MALIGNANT MELANOMA POSTERIOR SEGMENT, DEATH FROM METASTASIS, 57 CASES

<i>Years</i>	<i>Number of cases</i>	<i>Per cent</i>
0-1	17	29.8
1-2	16	28.1
2-3	11	19.3
3-4	6	10.5
4-5	2	3.5
5-6	3	5.2
6-7	1	1.8
7-8	1	1.8
TOTAL	57	100.0

MISTAKEN CLINICAL DIAGNOSES OF MALIGNANT MELANOMA OF THE CHOROID AND CILIARY BODY

Pathology laboratories occasionally receive eyes with the clinical diagnosis of malignant melanoma of the posterior segment in which no tumor is found. Reese¹ reported 25 eyes which did not contain a melanoma. Ashton² reported a series of 862 eyes which were removed with a clinical diagnosis of malignant melanoma of which 102 or 12 per cent proved to be non-malignant. Kirk and Petty³ reported 81 eyes

enucleated because of the possibility of melanoma but found not to contain tumors. Frayer⁴ made a histologic study of 24 eyes with non-neoplastic central elevated lesions resembling disciform degeneration. Thirteen (54 per cent) of these eyes were enucleated with the clinical diagnosis of malignant melanoma. Reese,⁵ analyzing 214 patients who had fundus lesions which made melanoma a suspect, found that 106 of these patients did not have a malignant melanoma as proven by the subsequent course of the disease. Inflammation or macular degeneration accounted for 60 per cent of the lesions simulating malignant melanoma.

Our laboratory has received 470 enucleated eyes with the clinical diagnosis or suspected diagnosis of malignant melanoma of the choroid or ciliary body. Upon histologic examination, 132 or 28.1 per cent of these eyes did not contain a malignant melanoma. Of the group of 132 mistaken diagnoses, a definite clinical diagnosis of malignant melanoma was made in 53 or 11.3 per cent, and a suspected diagnosis was made in 79 or 16.8 per cent. The mistaken diagnoses occurred in 66 males and 66 females. P32 studies were reported as positive in two cases, and negative in one. The average age at the time of enucleation was 57½, the youngest being 13 and the oldest 94 (Table 8).

TABLE 8. MISTAKEN CLINICAL DIAGNOSIS MALIGNANT MELANOMA POSTERIOR SEGMENT, AGE DISTRIBUTION, 132 CASES

<i>Age</i>	<i>Number of cases</i>	<i>Per cent</i>
10-19	5	3.8
20-29	4	3.0
30-39	5	3.8
40-49	17	12.9
50-59	24	18.2
60-69	39	29.5
70-79	26	19.7
80-89	10	7.6
90-99	2	1.5
TOTAL	132	100.0

In our series of 132 mistaken diagnoses of malignant melanoma of the posterior segment, glaucoma, retinal detachment, and uveitis were the most frequent histologic findings (Table 9).

In 31 cases, opaque media obscured the posterior segment. In eight cases diagnosed as malignant melanoma in the region of the macula

TABLE 9. HISTOLOGIC DIAGNOSES: MISTAKEN DIAGNOSIS
MALIGNANT MELANOMA, 132 CASES

1. Glaucoma	68 cases
2. Retinal detachment	58 cases
3. Uveitis	31 cases
4. Central vein thrombosis	8 cases
5. Disciform degeneration of the macula	6 cases
6. Phthisis bulbi	6 cases
7. Cataract	4 cases
8. Vitreous hemorrhage	4 cases
9. Massive subchoroidal hemorrhage	2 cases
10. Lens dislocated into vitreous	2 cases
11. Sympathetic ophthalmia	1 case
12. Retinoschisis	1 case
13. Cystoid cicatrix	1 case
14. Endophthalmitis	1 case
15. Equatorial scleral staphyloma	1 case
16. Ciliary staphyloma	1 case

in which there was adequate visualization of the fundus, the final histologic diagnosis was disciform degeneration of the macula in five, and retinal detachment involving the macula in three cases. In 33 cases, the eyes were blind and painful.

In the blind, painful eye where the fundus cannot be examined, enucleation is advisable because of the possibility of the eye containing an unsuspected malignant melanoma. All blind eyes should not, however, be removed because of the possibility of harboring a malignant melanoma. As Leopold⁶ has pointed out, where the ophthalmologist is reasonably sure of the cause of blindness and has or had recent access to a fairly satisfactory fundus examination, and if there are no other reasons for suspecting an intraocular malignant lesion, it does not seem reasonable to advise enucleation, particularly when the patient is comfortable.

Zimmerman⁶ states that tumor size gives some index of cell type, the smaller tumors usually being made up of spindle cells and the larger tumors containing a higher percentage of epithelioid cells. Because the prognosis for patients with tumors measuring less than five disc diameters is generally so favorable, he feels quite strongly that an ophthalmologist should be extremely certain of his diagnosis before recommending enucleation for a small lesion. He recommends that a patient with a small questionable lesion be placed under observation, and that serial photography, visual field studies, and any other diagnostic procedure considered helpful be employed until there is unquestionable evidence of progression and the clinical diagnosis of malignant melanoma is indisputable. Maumenee,⁷ discussing

the observation that there is little difference in the mortality rate between tumors two disc diameters in size and those three to four disc diameters in size, feels that this indicates that it is relatively safe to observe an atypical lesion for a while to be sure that it is growing before enucleating an eye. He suggests the use of careful sketches or fundus pictures in determining whether or not a questionable lesion is increasing in size. He feels that if this is done, fewer eyes will be removed in which disciform degeneration in the macula or inflammatory lesions in the periphery of the fundus are mistaken for melanomas.

CLINICALLY UNSUSPECTED MALIGNANT MELANOMA OF THE CHOROID AND CILIARY BODY

The ophthalmologist is reluctant to remove an eye even though blind with opaque media, if the external eye appears fairly normal. The incidence of unsuspected malignant melanoma, however, is sufficiently frequent to warrant consideration of enucleation if the media is opaque, and especially if the eye is blind and painful.

Pathology laboratories receive eyes for histologic examination which reveal intraocular neoplasms unsuspected by the ophthalmologist prior to enucleation. Makley and Teed⁸ reviewed 1000 cases of intraocular malignant melanoma and found 113 or 11.3 per cent unsuspected prior to enucleation. They stated that approximately 20 per cent of the eyes proven pathologically to contain malignant melanomas of the choroid or ciliary body had opaque media which prevented visualization of the tumor clinically. Kirk and Petty,³ reporting a series of 228 malignant melanomas of the choroid received at the pathology laboratories of the Illinois Eye and Ear Infirmary and the Research and Educational Hospitals of the University of Illinois, found that 24 of these tumors or 10.5 per cent were not suspected clinically. Reese,¹ in 1951, reported 18 cases of unsuspected malignant melanoma or 6.7 per cent in his series. Neame and Khan⁹ reporting on 402 eyes enucleated for glaucoma, stated that 40 or 10 per cent of these eyes contained a malignant melanoma of which 4 per cent contained an unsuspected malignant melanoma. Burch and Camp¹⁰ reported that 10 cases or 8.8 per cent of 113 histologically proven malignant melanomas were unsuspected prior to enucleation.

Sixty-eight or 16.7 per cent of our series of malignant melanomas of the posterior segment were unsuspected at the time of enucleation. One melanoma was discovered during the routine examination of the

eviscerated contents of an eyeball. Sixty-one or 89.7 per cent arose in the choroid, and seven or 10.3 per cent arose in the ciliary body. Twelve or 17.7 per cent showed external extension of the tumor. Surgical procedures had been instituted for the repair of retinal detachment in two cases. The tumors in our series occurred in 38 males and 30 females. The age at the time of enucleation was obtained in 64 cases, the average being 62, the youngest 33, and the oldest 85 (Table 10).

TABLE 10. UNSUSPECTED MALIGNANT MELANOMA OF THE POSTERIOR SEGMENT, AGE DISTRIBUTION, 64 CASES

<i>Age</i>	<i>Number of cases</i>	<i>Per cent</i>
30-39	3	4.7
40-49	9	14.1
50-59	13	20.3
60-69	18	28.1
70-79	15	23.4
80-89	6	9.4
TOTAL	64	100.0

The main clinical diagnoses submitted with the eyes in the unsuspected tumors are listed in Table 11. Fifty-four or 79.4 per cent had glaucoma, one had normal tension, and one hypotony. Retinal detachment and uveitis each occurred in 15 (22.1 per cent) cases. In 42 or 61.8 per cent, the fundus could not be visualized due to opaque media. In 39 or 57 per cent, the eyes were blind and painful. Forty-one were followed for five years or longer. Of these, 16 were living and well,

TABLE 11. MAIN CLINICAL DIAGNOSES IN 68 CASES OF UNSUSPECTED MALIGNANT MELANOMA

1. Glaucoma	54 cases
2. Opaque media	42 cases
3. Blind, painful eye	39 cases
4. Retinal detachment	15 cases
5. Uveitis	15 cases
6. Cataract	5 cases
7. Clear media	5 cases
8. Phthisis bulbi	3 cases
9. Intraocular hemorrhage	2 cases
10. Dislocated lens	1 case
11. Hypotony	1 case
12. Panophthalmitis	1 case
13. Traumatic rupture of the cornea	1 case
14. Brawny scleritis	1 case
15. Central vein thrombosis	1 case
16. Perforated corneal ulcer	1 case

16 had died from unrelated causes, and nine died of tumor metastasis of which eight or 19.5 per cent died within five years (Table 12).

TABLE 12. UNSUSPECTED MALIGNANT MELANOMAS OF THE POSTERIOR SEGMENT, DEATH FROM METASTASIS, 9 CASES

<i>Years</i>	<i>Number of cases</i>	<i>Per cent</i>
0-1	4	44.5
1-2	3	33.3
2-3	1	11.1
5-6	1	11.1
TOTAL	9	100.0

SUMMARY

Four hundred and six malignant melanomas of the choroid and ciliary body have been surveyed. Twenty-nine per cent of these tumors were limited to the choroid or the ciliary body, 71 per cent invaded adjacent intraocular tissues, 10.1 per cent had external extensions, and 16.3 per cent had metastasized. Three tumors occurred in the prepubertal age group.

In those eyes clinically diagnosed or suspected of harboring a malignant melanoma, the average age at the time of enucleation was 55½, there was external extension in 8.6 per cent, and 41.6 per cent of those followed for five years died of tumor metastasis.

In those eyes clinically unsuspected of harboring a malignant melanoma, the average age at the time of enucleation was 62, there was external extension of the tumor in 17.7 per cent, and 19.5 per cent of those followed for five years died of tumor metastasis. Of the malignant melanomas, 61.8 per cent had opaque media which prevented clinical examination of the fundus.

Of those eyes mistakenly diagnosed as harboring a malignant melanoma of the posterior segment, 23.5 per cent had opaque media preventing visualization of the fundus, and 25 per cent of the eyes were blind and painful. In eight cases, where there was adequate visualization of the fundus, the histologic diagnosis was disciform degeneration of the macula in five, and retinal detachment involving the macula in three.

Because small tumors carry a more favorable prognosis, small questionable lesions should be kept under observation until there is definite evidence of growth and tumor formation.

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DISCUSSION

DR. IRA S. JONES. "Twenty-eight per cent of the globes examined contained no melanoma." "Ten per cent of the globes examined showed external spread of the melanoma." Those two statements delineate very succinctly the extent of the problem.

The most important requirement in the diagnosis of malignant melanoma of the choroid is that the clinical criteria be made sufficiently broad so as to include all malignant melanomas. Otherwise, some equivocal cases may be placed in the non-melanoma group mistakenly and lead to increased danger of distant metastases and loss of life.

The next most important criterion should be that as many different kinds of confusing diagnoses as possible shall be separated off from the clinical diagnosis of malignant melanoma of the choroid. The reason for this is obvious. The more refined our diagnostic acumen, the fewer will be the number of eyes removed needlessly on the suspicion of malignant melanoma which actually harbor some other, less dangerous, condition. If a "wait and see" policy is adopted in dealing with borderline cases, then on the one hand, the lesion may manifest itself to be a melanoma at a considerably later date, or on the other hand, it may continue to camouflage its identity revealing only that it does not appear to be a melanoma. Those cases in which definite melanoma does not supervene, and in which the condition remains obscure, may never come to an accurate diagnosis and may never be analyzed and used to strengthen future diagnostic acumen.

The most informative and helpful course for future clinical perspicacity

is to analyze those globes removed for a suspicion of choroidal melanoma, and to correlate the clinical and histopathological findings. In this way, one can distinguish through the gradual accumulation of evidence definite clinical entities which are non-cancerous, and thereby minimize the number of eyes needlessly removed.

Dr. Windsor Davies has adopted this latter course with care, industry, and success, and his results speak for themselves.

DR. LORENZ E. ZIMMERMAN. I enjoyed this paper very much, and I regret that I did not have a chance to read it beforehand. I did not realize it was on the program.

Many of the facts Dr. Davies has presented coincide very precisely with observations we have been making. I would like to point out one practical difficulty in arriving at statistics of this sort. When dealing with an eye that has opaque media, an eye that has been enucleated, the clinician submitting the eye to the laboratory frequently tacks on as an added diagnosis, "possible intraocular tumor."

This makes it very difficult to arrive at statistics, so Dr. Andrew Ferry working at the AFIP, is going through all the cases in the registry to ferret out those cases in which the clinician observed a specific lesion, the media being clear, and, as a result of that lesion, made an erroneous diagnosis of malignant melanoma and needlessly enucleated an eye.

This is a very tedious and time-consuming job. I noted with interest that eight of Dr. Davies' cases fell into this category; five of which lesions were disciform degeneration and three were retinal detachment.

The problem of the differential diagnosis of retinal detachment is a very large one. Dr. Boniuk and I have just recently completed an analysis of 204 eyes that were submitted to the laboratory after one or more operations for reattachment of the retina. Some of these eyes had had three or four such operations. Out of these 204 eyes that had been treated surgically for retinal detachment, 60 were found to contain malignant melanomas; so this is no small problem. That is 30 per cent of the total series.

In addition to those 60 tumor cases, the problem of differential diagnosis of tumor came up in 14 others; that is, following a retinal detachment operation something happened which created a suspicion of melanoma, and the eye was then enucleated; but no melanoma was present. In some of these cases the retina has been successfully reattached. There was scarring and shortening of the sclera and dispersion of proliferation of pigment epithelium; these changes produced the picture of a phantom tumor. In other cases there was subretinal or subchoroidal hemorrhage that suggested a tumor, and in still others there was just marked buckling from the surgical procedure.

At any rate, this is one large and very important aspect of the problem of differential diagnosis of malignant melanoma.

With regard to clinically unsuspected melanomas that are found first in the laboratory, our percentage runs a little bit lower than Dr. Davies' figures. Approximately one in ten of the uveal melanomas that come into our laboratory has not been suspected clinically and is first suspected when the eye is examined in the laboratory.

One additional aspect of this problem that I think is of some significance is that at least three or four times a year an eye is sent to the laboratory as a "blind, painful eye," with nothing to indicate that the possibility of a melanoma had been considered clinically. When the pathologist in the laboratory takes the eye out of the bottle and looks at it, immediately he sees evidence of an extraocular extension, an episcleral nodule. It seems to me that the surgeon could have made the same observation at the time of operation just as well as we in the laboratory. So I would suggest that the surgeon should always look at the eye after he enucleates it and before he puts it in the bottle.

DR. ALSON E. BRALEY. I can't help but make a plea for better clinical diagnosis, as Dr. Jones did, but I wish each of you would learn to use the contact lens and the slit-lamp microscope in examining these eyes. You will learn a great deal more than you can by simple observation.

DR. A. D. RUEDEMANN. I would like to rise in defense of the consultants and the poor surgeons who do not have the eye in a bottle and a microtome to cut it in order to make a diagnosis.

Let us be straightforward about this. It is a very difficult diagnosis, and we are in the unfortunate position of a consultant when a patient is sent in. Here is an eye; we should say whether or not it should be removed. We are not all so fortunate to have men like Dr. Davies and Dr. Jones and the others around our laboratories.

I can cite instances where we removed an eye on the advice of three ophthalmologists. P32 studies were positive, and the pathology laboratory reported that there was no tumor found in the eye.

If anything travels faster through a hospital or a territory than the whisper that the surgeon removed a 20/20 or 20/40 eye in which there was no tumor, I can't imagine what it would be. Even the news of pregnancy doesn't travel as fast as that.

The truth of the matter was that this patient had his eye sectioned three times before the tumor was found. It was a very small, central melanoma. To verify the fact that it was a melanoma, the patient died in a matter of six to nine months with metastasis. So you see, the error can be on the other side of the fence.

This is not an easy diagnosis to make, and we are not sure even when we do P32 studies in every instance of retinal detachment. It is a very difficult procedure, and I am sure the 136 unsuspected eyes were probably those of

friends of the surgeons or were eyes that went along quietly without giving a great deal of trouble.

DR. DAVIES. First I wish to thank Dr. Jones for his remarks in opening the discussion of my paper and Drs. Zimmerman, Braley, and Ruedemann for their comments. The problem of differential diagnosis in many unsuspected and mistakenly diagnosed malignant melanomas of the posterior segment has been brought home to me during my years in the practice of clinical ophthalmology. This paper was presented to statistically survey some of these problems.