Internal resection of posterior uveal melanomas

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Abstract

***Aims*—To evaluate the safety and efficacy of internal resection in the treatment of malignant melanoma of the choroid.**

***Methods*—32 consecutive patients with histopathologically proved malignant choroidal melanomas were treated with internal resection. 29 of the 32 (90.6%) tumours were within 2 disc diameters of the optic nerve or fovea. The surgery was performed at two university centres by one of the authors. Follow up was between 1 and 85 months (mean 40.1 months).**

***Results*—Three patients developed distant metastases and died of malignant melanoma (metastatic and mortality rate 9.4%). In one case, distant metastases developed in association with an intraocular recurrence. There have been no other intraocular recurrences. The most common postoperative complication was vitreous haemorrhage, which occurred in 12 patients (37.5%); cataract occurred in eight eyes; and three patients developed retinal detachment postoperatively. Three of the operated eyes have been enucleated (9.4%); a total of four (12.5%) have lost light perception. 10 patients (31.2%) had visual acuities of 6/60 or better and 18 of 32 (56.3%) were between 6/120 and light perception.**

***Conclusion*—These data suggest that the internal resection of posterior uveal melanomas is a reasonable globe saving management option. This treatment modality is particularly well suited to elevated tumours in close proximity to the optic nerve or fovea.**

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Uveal melanomas are the most common primary intraocular malignancy and, other than the skin, the uvea is the site most commonly affected by melanoma. In the United States, the incidence of ocular melanoma is approximately six cases per million population per year with a median age of onset of 55 years.[1 2] With uveal melanomas, distant metastases peak 2–3 years after enucleation and patients with distant metastases seldom survive longer than a year.[3] Many factors have been suggested as being of prognostic value[4] but larger tumour size,[5 6] anterior tumour margin,[6–8] cellular pleomorphism,[6 9] and extrascleral extension[10 11] have consistently been associated with the occurrence of distant metastases and death.

The optimal management of ciliary body and choroidal melanomas has long been a matter of controversy and the indications for various treatment modalities are continuously being refined and modified.[12 13] For many years, enucleation of the affected eye was generally considered to be the only appropriate management for the patient with a posterior uveal melanoma.[14] In 1979, Zimmerman and McLean challenged the effectiveness of enucleation for the prevention of metastatic disease and proposed that enucleation may somehow promote or accelerate metastases.[3] This controversy over enucleation has led to a trend away from enucleation and towards the increasing use of more conservative therapeutic methods. Depending on the size and extent of the melanoma, there are advocates of periodic observation, photocoagulation, radiotherapy, local tumour resection, and enucleation. The two most frequently employed treatment methods today are enucleation and episcleral plaque brachytherapy.[15] The Collaborative Ocular Melanoma Study (COMS) has been organised to address some of these complex treatment questions.[16]

Until the results of this large prospective randomised clinical trial are published or, more specifically, until one treatment modality is shown to be definitively superior to the others, we have to rely on the survival data reported for the large series of the separate treatment modalities to make our judgments. Looking critically at those data, it would appear that enucleation, radiotherapy, and even local resection have similar rates of metastases and death[17–19]; that is to say, depending on the subpopulation looked at, a 5 year survival rate of between 65 and 93%.[5 10 14 20–32] We present here our data on 32 consecutive patients with pathologically confirmed uveal melanomas treated with internal resection and followed for a mean of 40.1 months (range 1–85 months). This is the longest follow up and the largest series thus far reported on this novel treatment modality that began in 1984.

Patients and methods

The patient and tumour characteristics are given in Tables 1 and 2. All surgery was performed by one of the authors (GAP). The 32 patients included in this analysis were enrolled consecutively and no cases were excluded. There were 20 males (62.5%) and 12 females (37.5%). They ranged in age from 25 to 81 years with a mean age of 54.8 years and were followed for a mean of 40.1 months (range 1–85 months).

Almost all patients in our study population had posterior tumours, 29 (90.6%) of which were within two disc diameters of the optic nerve or fovea. All had confirmed malignant uveal melanomas with a mean largest basal

Table 1 Patient and tumour characteristics

Case No	Age	Sex	Maximum basal diameter (mm)	Tumour height (mm)	Cell type	Tumour location (≤3 mm to optic nerve or fovea)	Follow up (months)	Visual acuity		Complications		Notes
								Preop	Final	Early	Late	
1	70	M	4.5	8.9	Epithelioid	yes	16	6/18	CF 3'	Elevated IOP		Liver metastases 16 months postop. Death 2 years postop
2	72	F	9	3.7	Mixed	yes	5	6/30	HM 2'	Vitreous haemorrhage		
3	43	M	6	6.5	Spindle B	yes	6	6/7.5	CF 2'	Elevated IOP, vitreous haemorrhage	Corneal ulcer	
4	64	F	4.5	2.0	Mixed	yes	71	6/60	NLP	Vitreous haemorrhage	Phthisis	History of PDR
5	29	F	5.0	2.5	Mixed	no	22	6/12	6/7.5			
6	62	M	9	3.1	Mixed	yes	60	6/90	CF	Elevated IOP, vitreous haemorrhage	Worsening of preop cataract Localised inferior tractional RD	
7	44	F	5.8	3.1	Mixed	yes	24	6/60	CF		Cataract	
8	39	M	7.5	2.9	Spindle B	yes	79	6/7.5	6/60			
9	77	F	12	2.6		yes	43	CF 5'	CF 3'			History of geographic atrophy 2° to ARMD
10	59	F	4	4	Spindle B	no	10	6/6	6/7.5	Minor vitreous haemorrhage	Worsening of existing cataract	
11	43	M	9	6.5	Mixed	yes	58	6/60	LP	Cataract, residual tumour requiring reoperation	Band keratopathy, hypotony	
12	46	M	8	10	Mixed	yes	1	6/60	LP	Vitreous haemorrhage		Subsequently convinced by another physician to enucleate
13	46	M	9	7	Mixed	yes	21	6/15	CF 1'		Vitreous haemorrhage, retinal detachment	
14	63	M	8	5	Mixed	yes	57	6/90	NLP	Vitreous haemorrhage	Cataract	Enucleated because of suspected recurrence. Pathology proved negative.
15	77	M	10	4.5	Mixed	yes	85	6/18	HM 5'		Worsening cataract	
16	33	M	12	6.6	Mixed	yes	48	6/12	HM 3'		Cataract	
17	28	M	6	2	Spindle B	yes	40	CF 1'	CF 1'			
18	36	M	12	9	Spindle B	no	5	CF 3'	HM 1'		Vitreous haemorrhage	
19	25	M	4	5		yes	9	6/60	6/30			
20	60	F	15	flat	Spindle B	yes	83	6/15	6/60			
21	76	M	4.5	2	Mixed	yes	28	6/120	CF 5'			
22	54	M	9	4	Spindle B	yes	17	6/60	CF	Vitreous haemorrhage		
23	57	M		5	Mixed	yes	62	6/12	NLP	Submacular haemorrhage		
24	53	F	8	12	Spindle B	yes	57	6/24	6/60			Intraocular recurrence, liver metastases. Death after 57 months
25	61	M	8	9	Mixed	yes	76	6/15	NLP		PVR, RD. Blind painful eye	Enucleated
26	68	M	3	2	Mixed	yes	58	6/7.5	6/12		Cataract	
27	40	F	5	4	Mixed	yes	72	6/9	6/60			
28	54	F	3	5	Spindle B	yes	65	6/21	CF			
29	71	F	6	2	Spindle B	yes	84	6/12	6/60		Epiretinal membrane	Liver metastases. Death after 84 months
30	66	M	15	3	Mixed	yes	5	6/6	6/24			
31	81	M	9	9	Epithelioid	yes	10	6/60	HM 4'	Vitreous haemorrhage	Extruded scleral buckle	
32	55	F	18	7	Epithelioid	yes	5	6/30	6/120	Vitreous haemorrhage		

diameter of 8.0 mm (range 3–18 mm) and a mean height of 5.3 mm (range flat to 12.0 mm). The original COMS criteria were used to classify the tumours by size with 26 of the melanomas falling into the medium category, four small, and two large. For inclusion, they had to have no evidence of distant metastases or extraocular extension. As the uvectomy procedure is done under hypotensive anaesthesia—that is, a systolic blood pressure of 100 mm Hg to reduce the risk of bleeding complications, patients with systemic diseases that would make them a poor anaesthetic risk were not offered this treatment. Patients were told of the risks and alternatives and a detailed informed consent was obtained.

Preoperatively, patients had a complete anterior and posterior segment eye examination that included careful indirect ophthalmoscopy and transillumination. The dimensions and echographic characteristics of the tumour were obtained with A and B-scan ultrasonography. The systemic evaluation was carried out by a consulting oncologist and included, in all cases, liver function tests and a chest *x* ray and, in many cases, was supplemented by head computed tomography (CT) and/or magnetic resonance imaging (MRI) scans.

Postoperatively, patients had a complete eye examination on days 1 and 7. They were then followed monthly for 3 months, and at 6 month intervals thereafter. For evaluation of distant

Table 2 Summary of patient and tumour data

Patient characteristics:	*Mean*	*Range*
Age (years)	54.8	25–81
Follow up (months)	40.1	1–85
	n	%
Male	20	62.5
Female	12	37.5
Tumour characteristics:		
Location ≤3 mm from the optic disc or fovea	29	90.6
Size		
Small	4	12.6
Medium	26	81.2
Large	2	6.3
Pathology	30	
Spindle B	10	33.3
Mixed	17	56.7
Epithelioid	3	10
Metastases/death		
Intraocular recurrence	1	3.1
Distant metastases	3	9.4
Metastatic death	3	9.4
Visual acuity at last follow up		
≥6/60	10	31.2
<6/60–LP	18	56.3
NLP	4	12.6
Enucleated	3	9.4

metastases, the patients were also seen and examined by an internist or oncologist every 6 months and screened with at least liver function tests and chest *x* rays.

SURGICAL TECHNIQUE

The following technique has evolved from previously described methods[33–39] and is our currently preferred method of resecting posterior tumours (Fig 1). Before entering the eye, a 360 degree peritomy is performed and the sclera and vortex veins are carefully examined for extraocular extension of melanoma. If none is found, we proceed with a limited standard posterior three port pars plana vitrectomy and, if necessary, pars plana lensectomy. Whenever possible, the vitrector and light pipe are positioned opposite the tumour. We try to retain the anterior vitreous during the tumour resection in order to trap tumour cells that are liberated during the melanoma excision and removal. With diathermy and intraocular scissors, an arcuate retinotomy is then created and dissected free of the tumour in an anterior to posterior direction. Diathermy and argon laser endophotocoagulation are applied over the tumour surface and margins and, under hypotensive anaesthesia (systolic blood pressure of 100 mm Hg or below), all visible tumour and a surrounding safety margin of perhaps 0.5 mm are resected with the vitrector down to

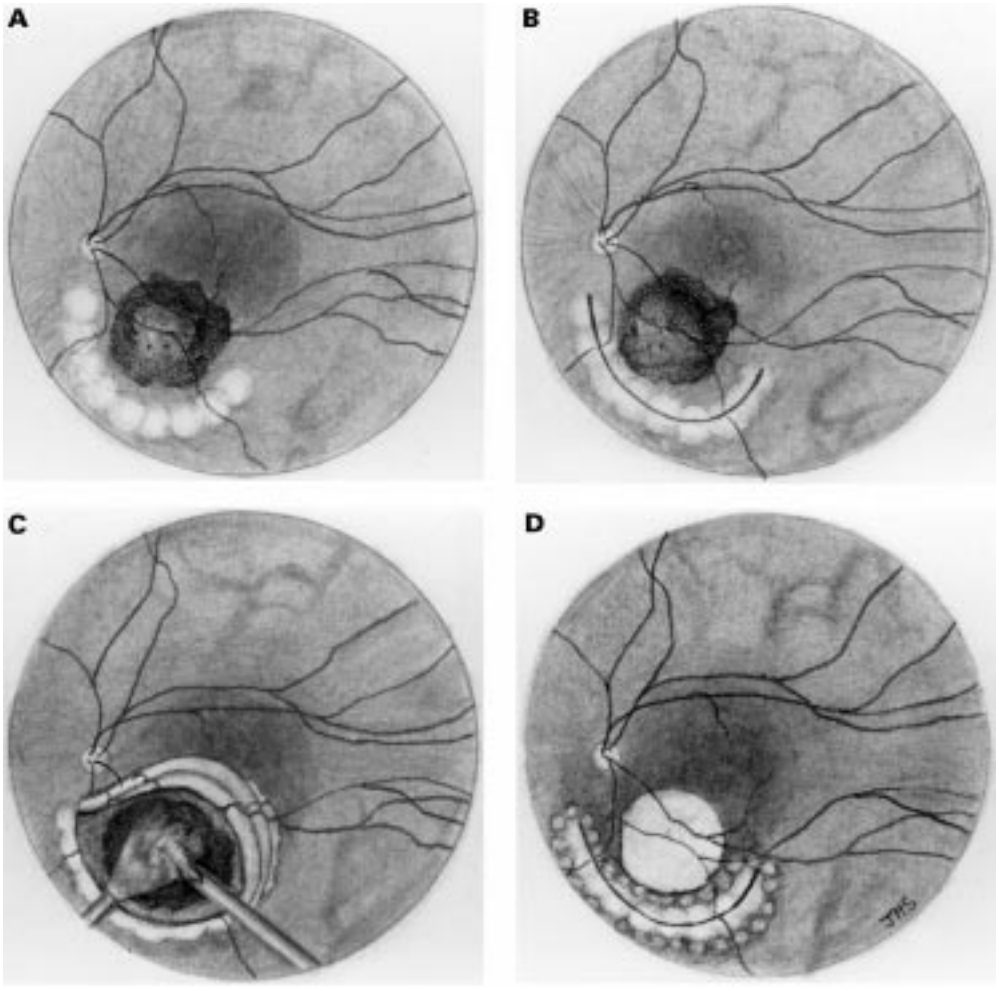

Figure 1 Schematic diagram illustrating the salient features of the surgical technique. (A) Endodiathermy is applied in an arcuate fashion to the retina peripheral to the tumour. (B) A retinotomy is created with intraocular scissors and dissected free of the tumour in an anterior to posterior direction. (C) Diathermy and argon laser endophotocoagulation are applied over the tumour surface and margins and, under hypotensive anaesthesia, all visible tumour is resected with the vitrector down to bare sclera. (D) The retinal flap is reposited and an air-fluid exchange performed. Laser is applied to the edges of the retinotomy and the eye is filled with silicone oil (5000 centistokes).

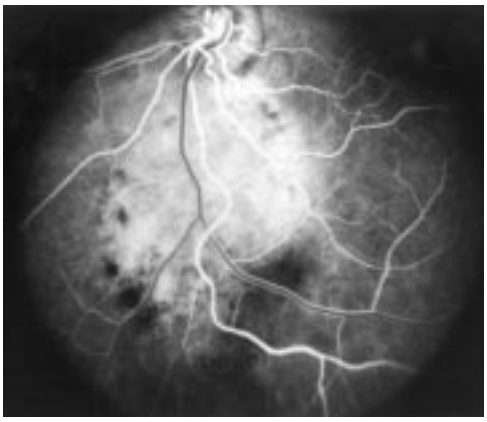

Figure 2 Arteriovenous phase fluorescein angiogram of the patient's left eye in 1987 demonstrating hyperfluorescence of a small choroidal tumour.

bare sclera. Further photocoagulation is then applied to the scleral bed. The vitrectomy is completed, removing the remaining anterior vitreous. The retinal flap is reposited and an air-fluid exchange performed. Laser is applied to the edges of the retinotomy and in a scatter fashion around the rest of the fundus. The eye is filled with silicone oil (5000 centistokes) and an encircling number 20 band is placed and secured with previously placed, partial thickness 5-0 Dacron mattress sutures. The silicone oil is retained for a minimum of 6 months and a maximum of 2 years.

Case report

A 55 year old white woman presented to us with a 6 month history of flashes, glare, and a veil in her left eye. She had been seen elsewhere in 1987 and found incidentally to have choroidal naevi in both eyes (Fig 2) but was lost to follow up. She was referred to us in August 1995 and had a large amelanotic choroidal mass abutting on the inferior optic nerve with an associated inferior serous retinal detachment (Fig 3). The tumour measured approximately 18 mm in diameter and had a height, on B-scan, of 7 mm with low internal reflectivity. Interestingly, in her asymptomatic right eye she had an amelanotic flat choroidal lesion that was approximately 6 mm in diameter (Fig 4). She

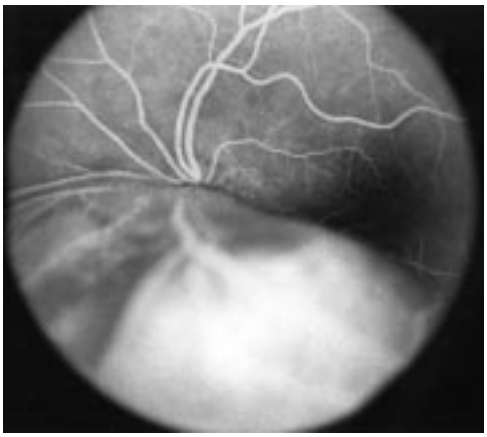

Figure 3 Arteriovenous phase fluorescein angiogram of the patient's left eye at presentation to us in August 1995, demonstrating early hyperfluorescence of a large choroidal melanoma.

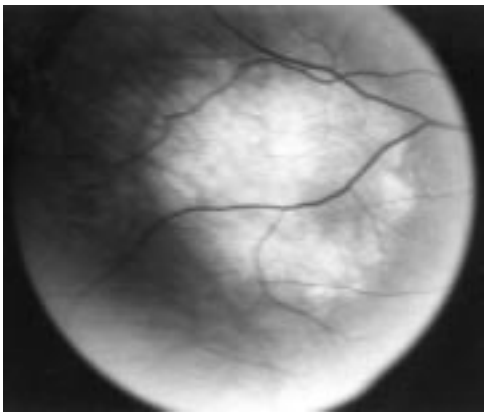

Figure 4 Fundus photograph of the patient's asymptomatic right eye at presentation to us in August 1995, demonstrating an amelanotic flat choroidal lesion temporal to the macula.

was seen by an oncologist and investigated for a primary malignancy elsewhere, but these investigations all proved negative. Also of note, her liver function tests, chest *x* ray, and CT scan showed no evidence of distant or extraocular extension of her melanoma. She was told of her risks and options and offered internal resection which was done under a retinal flap on 1 September 1995.

The pathology is shown in Figure 5. The specimen was spun down from the vitrectomy cassette and cut. The low power view shows clumps of tumour cells and scattered fragments of normal retina and choroid. The higher power view better demonstrates the epithelioid melanoma cells. She has thus far had an uncomplicated postoperative course. Figure 6 gives the appearance of her fundus on 15 February 1996. The retinal vessels are intact and run over the scleral bed from which the tumour has been resected. Her best corrected vision, aphakic, and with silicone oil, was 6/120 but she was satisfied with that and happy to have kept her eye. Her retina remains flat and there has, as yet, been no evidence of recurrent disease.

Results

All patients had histopathologically confirmed malignant uveal melanoma: 17 of the mixed type, 10 of the spindle B type, and three epithelioid cell type.[40]

Final visual acuity ranged from 6/7.5 to no light perception (NLP). Ten patients (31.2%) had visual acuities 6/60 or better, 18 of 32 (56.3%) were between 6/120 and light perception, and four were NLP. These guarded visual results must be interpreted in the context of the fact that 29 of 32 (90.6%) of these patients had tumours that extended to within two disc diameters of the optic nerve or fovea.

This complex surgery was unfortunately not without its complications. The most common adverse event was the development of a postoperative vitreous haemorrhage, which occurred in 12 (37.5%) of our patients. Because blood is immiscible with silicone oil, postoperative haemorrhage is typically compartmentalised in a preretinal location. This can lead to traction and retinal detachment,

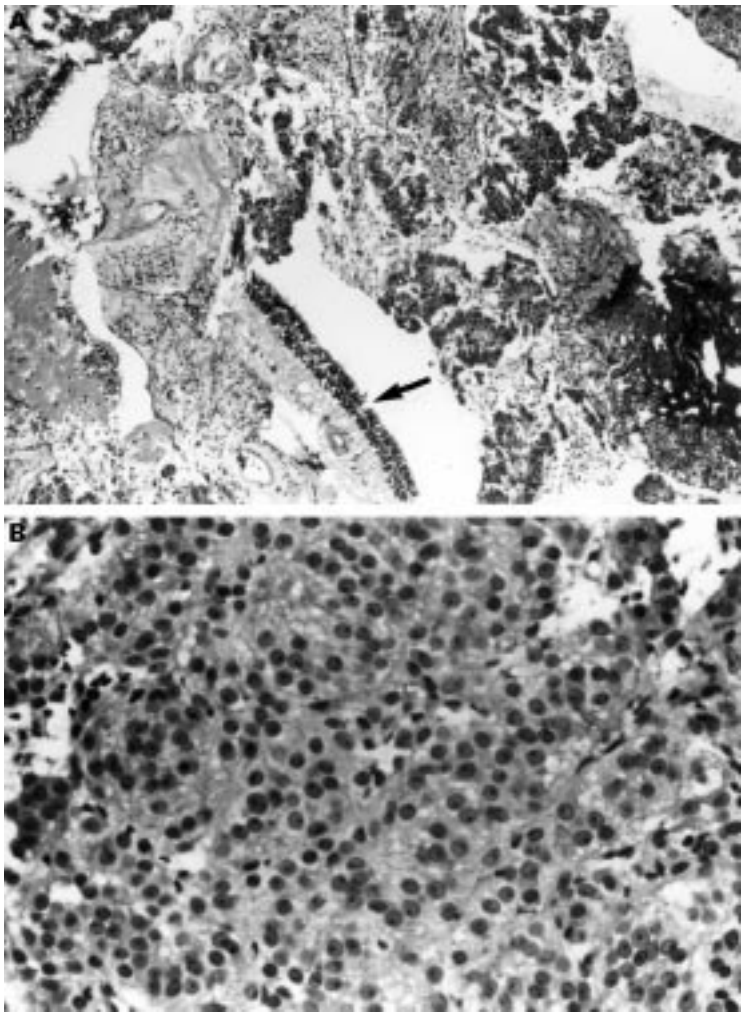

Figure 5 (A) Histological section of the material collected and spun down from the vitrectomy cassette demonstrating clumps of epithelioid melanoma cells together with bits of normal retina (arrow) and choroid (haematoxylin and eosin, original magnification, ×100). (B) Higher power view of a clump of tumour cells consisting almost exclusively of epithelioid melanoma cells (haematoxylin and eosin, original magnification ×400).

which occurred in two of these patients. In the remaining 10, the haemorrhage cleared without incident within 3 months. Eight eyes that were phakic postoperatively developed a cataract during the follow up period. A total of three patients developed a retinal detachment; three had elevated intraocular pressure; and one patient required early repeat surgery for what was judged to be residual tumour. The few other lower incidence complications are given in Table 1.

In this series, three patients (9.4%) died of metastatic disease over the period of observation. These three patients were all found to have evidence of liver metastases, one in association with an intraocular recurrence, and succumbed to their disease at 22, 57, and 84 months postoperatively. Three of the operated eyes (9.4%) were ultimately enucleated. One was removed because it was blind and became painful. A second eye was subsequently enucleated because of a suspected recurrence but the histopathology that was done proved to be negative. The third was enucleated only 6 weeks postoperatively because the patient was left with poor vision and became uncomfortable with the idea of retaining an eye that had harboured a malignant tumour. The histopathology that was done on this eye is the subject of another paper and showed no evidence of residual viable tumour cells.

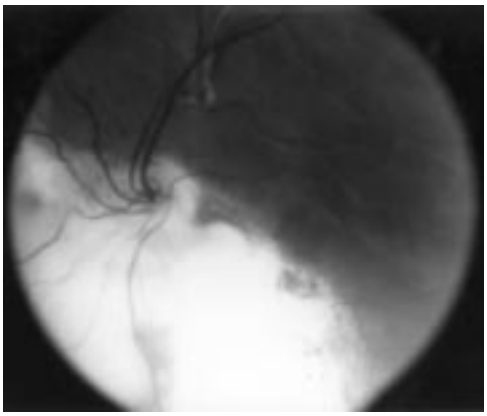

Figure 6 Fundus photograph of the patient's left eye 6 months postoperatively shows the intact retinal vessels running over the scleral bed from which the tumour has been resected.

Discussion

Assuming that survival rates are comparable among the different treatment options,[17–19 31] then one should next consider the functional success and limitations of the chosen treatment modality. With plaque radiotherapy, we know that as many as 56% of tumours will not show clinical regression[21 41] and those that do regress do so approximately 6–9 months after treatment and may continue to regress for more than 4 years.[18 23 42 43] Most uveal melanomas treated with brachytherapy regress incompletely and persist as minimally to moderately shrunken residual lesions.[21–23 27 28 42–45] Indeed, Augsburger and coworkers have demonstrated that rapid and more complete regression of choroidal malignant melanoma after cobalt-60 plaque radiotherapy is an unfavourable risk factor for death from metastatic melanoma.[45] As many as 17% of successfully irradiated tumours eventually reactivate and grow.[24 25 41] Such a recurrence may take months or even years to manifest itself.[22] In the 7.6–46% of irradiated eyes that are enucleated and examined pathologically,[23 25 42 46–48] it is common to find viable tumour cells and active mitotic figures on histopathological section.[21 25 42] It is unclear what the implications and the importance of these time delays and these findings are on patient survival.

In many areas, the preservation of visual acuity after radiation therapy is limited by complications, such as vitreous haemorrhage, cataract, retinal detachment, rubeosis iridis, radiation retinopathy, and optic neuropathy.[28 42 48–51] The latter occurs eventually, in some form, as often as 82% of the time when juxtapapillary tumours are treated.[46] Additionally, it would appear that there are intrinsic tumour factors, both during the growth and regression of the tumour, that can produce significant ocular morbidity.[27] Regardless of the method of radiotherapy used, 35.2–67%[25 28 41 42 47–49 52 53] of eyes become

legally blind, depending on the length of time that they are followed. Radiation vascular complications have a mean latency of approximately 2–3 years and occasionally are not manifest for 20 years after treatment.[54] Tumours in close proximity to the optic nerve or fovea and with a greater tumour height have an especially poor prognosis.[46 47 49 53] These complications, which are largely secondary to radiation vasculopathy, take time to appear and worsen the longer that patients are followed.[22 41 49 52] These nearly universal findings severely limit our ability to productively treat tumours close to the optic nerve with radiation. This is to say nothing of the risks to healthcare personnel who are repeatedly exposed to the harmful effects of radiation in the care of these patients. The lack of a pathological diagnosis is disconcerting to many patients and practitioners and it limits our ability to give the patient accurate prognostic information and, in the future, may limit the adjunctive use of immunotherapy.[55 56] Therefore, studies of the natural history of malignant melanomas without a knowledge of cell composition may be inaccurate.

The use of external resection has serious limitations as well. The use of an external approach is technically demanding, particularly for posterior tumours, and not without significant complications and visual outcomes not unlike those achieved with other globe saving procedures. In Peyman and associates' long experience with eye wall resection, an enucleation rate of 11/34 (32.3%) is quoted and 24 of 34 (70.6%) patients ended up with 20/200 or worse vision.[32] Shields *et al* report a vitreous haemorrhage rate of 83%, a retinal detachment rate of 28%, and cataract formation in 34%.[30] Perhaps most importantly, residual and recurrent tumours appear to be an issue much more often in cases of external rather than internal resection.[30 32] Damato and coworkers, in their large experience, describe residual or recurrent disease occurring in 81 of 310 patients (26%) treated with external resection and found that the rate of metastatic death in that subgroup (27%) was more than twice that of the remainder of the group (13%) without those complications.[57 58] They also found that histological assessment of surgical clearance was not reliable in predicting local tumour recurrence from microscopic disease.[57] As of 1986, they have routinely used adjunctive plaque radiotherapy, laser photocoagulation, or cryotherapy to reduce the risk of local tumour recurrence and metastases[57 58] and can therefore expect a different set of complications to occur with time.

Other treatment modalities such as laser photocoagulation have limited applications. Laser is probably best suited for treating flat, posterior melanotic lesions or in the adjunctive treatment of previously irradiated tumours.[12 44] Transpupillary thermotherapy is a promising newer technique that awaits longer follow up but appears to be best suited for the treatment of smaller posterior melanomas.

These difficulties and limitations led to the development, over 13 years ago, of internal resection as an alternative for uveal melanoma patients who were poor candidates for other conservative modalities.[37–39] The technique began as an adjunct to external resection[35] and evolved to its present incarnation, as a uvectomy done under a retinal flap with preservation of the overlying retina.[33 34] It has the advantages of more complete tumour excision with the subsequent availability of histopathological examination and diagnosis. It is, moreover, a technique that can be done by an ocular oncologist trained in modern vitreoretinal surgical techniques and is thus more accessible than techniques such as charged particle irradiation which is available at only a handful of centres in North America.

With an average of nearly 3.5 years of follow up, our results, while still preliminary, appear to be no worse than with any other treatment modality. Moreover, our experience thus far does not support the contention that surgical manipulation of malignant uveal melanoma promotes metastases. It is a technique that certainly warrants further study and investigation. Although longer follow up is still needed, we feel that, with more than 10 years' experience, internal resection is a reasonable and safe alternative to the management of posterior uveal melanomas. Approximately 50% of uveal melanomas occur less than 3 mm from the optic nerve or fovea[18] and we feel that ours is a technique that is particularly well suited to the treatment of tumours that are in close proximity to the optic nerve or fovea and that are of greater elevation.

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