Primary iris melanoma: diagnostic features and outcome of conservative surgical treatment

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Abstract

Aims—To describe features influencing the management of primary iris melanoma and report the outcome of conservative surgical treatment of patients diagnosed with this condition in a tertiary referral academic setting over a 20 year period.

Methods—Retrospective non-comparative case series of consecutive patients diagnosed with iris melanoma from 1980–2000 using medical records from the University of Sydney Department of Ophthalmology and NSW Cancer Registry

Results—51 cases were identified. The most common presentation was growth of a previously noted pigmented lesion. Initial management was either observation or local resection (two had enucleations) with iris reconstruction where possible (23.8%). The mean follow up was 8.7 years (range 1–17 years). Vision of 6/12 or better was maintained in the majority (78.6%) treated by local resection. Pupil reconstruction significantly reduced reported postoperative glare symptoms. Four patients had features suggestive of local recurrence and there was no documented metastatic disease or death from iris melanoma in this series. Histologically, the majority were spindle B cell melanomas. Clinical features including prominent tumour vascularity, rapid growth, and heterogeneous pigmentation were each significantly associated with an epithelioid cell component. Involvement of the iridocorneal angle was frequently associated with ciliary body invasion.

Conclusions—Management decisions for iris melanoma will depend on the clinical features. Mixed or epithelioid histology is more likely in the presence of two or more of the features of malignancy and may justify earlier intervention. When treatment is undertaken, local resection achieves long term tumour clearance with an acceptable morbidity. In resecting iris melanoma, careful assessment for iridocorneal angle involvement is important in treatment planning. Iris reconstruction has a useful role in reducing postoperative photophobia.


Melanoma arising in the iris is rare comprising 4–5% of all uveal melanomas.1 The management of iris melanoma is controversial as most lesions are diagnosed in middle aged patients when the lesions are small, the patients asymptomatic with excellent vision, and the natural history in the majority is benign slow growth. Iris melanomas usually grow locally into the anterior chamber or along the iris surface and commonly invade the anterior chamber angle and anterior ciliary body by local extension. A recent study has identified clinical features associated with a less favourable prognosis while other studies have found that, on histopathology, a subset of lesions involving an epithelioid component (that is, mixed or epithelioid melanomas), can behave more aggressively.2 It is reported that, overall, 3–5% of iris melanomas will metastasise after 10 years, whereas for mixed and epithelioid tumours, Geisse and Robertson have found that 11% and 7% respectively will eventually metastasise.3 Recognition of clinical features associated with these more aggressive melanomas may have implications for earlier intervention.

Clinicopathological studies have determined that many excised iris tumours are naevi and borderline lesions rather than frank melanoma. Identification of those clinical features suspicious for melanoma remains challenging.4 5 A number of studies have reported that documented growth, basal diameter >3 mm, abnormal vasculature, pigment dispersion, satellite lesions, and tumour related symptoms are highly suspicious for melanoma (spindle, mixed, or epithelioid) while ectropion uveae, anterior chamber angle involvement, slow growth, and even glaucoma do not always clearly distinguish reliably between naevi and melanomas.6 7 Those features associated specifically with the more aggressive epithelioid or mixed cell histology remain to be determined.

The generally more benign prognosis and historically high false positive diagnosis rate have led to a trend in recent years towards conservative management of suspect melanocytic iris tumours. This involves periodic observation of the lesions and interventions aimed at preserving the eye and vision if there is evidence of more aggressive behaviour; enucleation now being reserved for large unresectable tumours. Over the past 20 years advances in microsurgical technique, such as introduction of the partial lamellar flap, have improved access to the iris, anterior chamber angle, and ciliary body.8 9 10 These techniques have allowed more precise tumour resection to become possible, minimising trauma to the eye and greatly reducing the complication rate. In more recent years, advanced tissue reconstructive techniques involving corneoscleral tectonic grafting and pupil reconstruction have further improved the outcome in selected cases.1 However, only a limited number of studies have reported the long term outcomes of such an
approach for the management of iris melanoma.\textsuperscript{2} 12-16

In this article we attempt to delineate features of importance in the management of iris melanoma. In particular, we examined clinical factors associated with a less favourable histology (that is, epithelioid cell component) and report the outcome of local resection of a consecutive series of 51 patients seen over a 20 year period at the University of Sydney, Department of Ophthalmology.

Materials and methods
Retrospective review of records of the University of Sydney, Department of Ophthalmology at Sydney Eye Hospital between 1980 and 2000 identified 51 consecutive patients with the clinical diagnosis of primary iris melanoma for analysis. Correlation with the NSW Cancer Registry to identify melanoma associated deaths among these patients was also undertaken.

In agreement with other series, iris melanomas or lesions suspicious for iris melanoma were diagnosed clinically in the presence of an iris melanocytic lesion that locally replaced iris stroma, and/or was $>$3 mm in diameter or 1 mm thick and/or was associated with one or more of the following features including prominent vascularity, ectropion uveae, secondary cataract, secondary glaucoma, and evidence of documented growth.\textsuperscript{2} 8-3 These patients were included in the series. Melanomas arising primarily from the ciliary body were excluded owing to their more aggressive behaviour compared with primary iris melanoma. Over the study period, 237 patients were referred to the unit with other melanocytic lesions not fulfilling these criteria for iris melanoma. (including iris naevi, iris cysts, and essential iris atrophy) and were excluded.

The following data were documented in the medical records: tumour related symptoms, best corrected visual acuity, intraocular pressure, hyphaema, maximal basal tumour dimension, satellite lesions, lesion pigmentation (either homogeneously pigmented or variably pigmented), prominence of tumour vasculature, pigment dispersion, iridocorneal angle involvement by tumour (involvement was defined as the presence of tumour cells encroaching on the iris root plus or minus trabecular meshwork plus or minus anterior ciliary body), pupil distortion, ectropion uveae, and sectoral cataract. Documented growth was present if there was documented evidence demonstrating increase in any dimension of the lesion. This growth was further defined as rapid if the increase in dimension occurred over less than 3 years.

Lesions with features suggesting aggressive behaviour (that is, documented growth, large size ($>$3 mm basal diameter), prominent tumour vascularity, tumour related symptoms, increased intraocular pressure, satellite lesions, and ring melanoma pattern), were managed by surgery consisting of local resection if fulfilling the criteria described below or enucleation for larger/diffuse lesions or ring melanomas. Lesions suspicious for iris melanoma were documented and observed with serial photography at frequent intervals (3–6 months). Once documented growth or other features suggesting progression (for example, increasing intraocular pressure) was established, the possibility of melanoma was entertained and consideration given to local resection. In two patients the lesion was biopsied before making a management decision. All patients underwent systemic review before surgery. Local resection was attempted if the tumour was circumscribed, located within the iris with or without ciliary body involvement; involving the iris by not more than 5 clock hours; and where there was no evidence of extraocular extension. All surgery was performed by one surgeon (FB). In brief, surgery was performed under general anaesthesia with relative hypotension. Reverse Trendelenburg positioning was routinely employed. Surgical access involved raising a limbal based partial thickness corneoscleral lamella flap centred on the tumour, the most posterior extent of which having been defined by transillumination. The iris tumour was then excised under the flap, obtaining a surgical margin of macroscopically uninvolved tissue. If there was invasion of anterior ciliary body involvement, the tumour was routinely removed by en bloc excision of the iris tumour, trabeculum, and the anterior ciliary body back to the ciliary sulcus. In more recent years, with the advent of better microsurgical instrumentation, most cases have involved larger superficial flap dissections extending well into the clear cornea and the flap edge being at least 4–5 mm from the tumour margin. In many cases requiring more extensive excisions ($>$3 clock hours) or with bulky ciliary body involvement, a Fleiringa ring was employed to support the globe. In such cases, a trans pars plana vitrectomy port was also created before opening the globe. If there were signs of positive vitreous pressure prior to tumour excision, a prophylactic vitrectomy was then performed via the preformed port. Since 1992, where possible, the pupil was reconstructed and iris defect closed using interrupted 10/0 Prolene sutures.

Univariate analysis with Fisher’s exact test (significance level of 0.05) assessed for the association between unpaired data.

Results

CLINICAL FEATURES AT PRESENTATION
Of the 51 patients identified, there were 24 males and 27 females. Reasons for presentation are described in Table 1. Ages ranged from 7 to 76 years with a mean of 45.0 years. Most patients had excellent best corrected visual acuity in the affected eye at the time of diagnosis; 45 (88.2%) had visual acuity of 6/9 or better. The mean intraocular pressure was 13.2 mm Hg in the involved eye. Eight (15.7%) had intraocular pressure greater than 21 mm Hg, the highest being 30 mm Hg. All were unilateral cases, with 31 affecting the left eye and 20 affecting the right eye.
In 40 (78.4%) eyes, tumour involved the inferior iris; eight (15.7%) were located in the superior iris; three (6.8%) were diffuse. The tumour shape was nodular in 78.4% and flat in 21.6%. The mean tumour base diameter was 6.7 mm (range 3–11 mm), and the mean number of clock hours of iris involvement was 4.3 (range 1–12). Thirty three (64.7%) had involvement of the iridocorneal angle of whom 12 (23.5%) had clinical evidence of frank ciliary body involvement. Other clinical features are included in Table 2 and a comparison of this cohort with other series reported since 1977 in Table 3.

MANAGEMENT

Twenty seven patients (52.9%) were initially managed by observation alone. One of these patients had a peripheral iridectomy biopsy which showed predominantly spindle A cells and consequently was managed with observation as well. One patient with 360 degree angle involvement by tumour and another with biopsy proved iris melanoma and extraocular extension underwent primary enucleation as initial treatment.

The remaining 22 (43.1%) had primary local resection by iridocyclotrabeculectomy or similar procedure. Two of these patients were macroscopically incompletely resected. One of these patients had an enucleation within days of the primary procedure while in the other, an elderly male with an only eye, enucleation was of the primary procedure while in the other, an only eye, enucleation was declined.

Table 3 Clinical and pathological features—reported results since 1977

<table>
<thead>
<tr>
<th>Author</th>
<th>No</th>
<th>Follow up</th>
<th>Location</th>
<th>Tumour dimension†</th>
<th>Histopathology‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forrest et al ⁵⁴ ¹</td>
<td>107</td>
<td>(9–14)</td>
<td>LCB</td>
<td>(2.0)</td>
<td>11.2</td>
</tr>
<tr>
<td>Kara ²</td>
<td>35</td>
<td>5</td>
<td>LCB, C</td>
<td>(1.8)</td>
<td>8.6</td>
</tr>
<tr>
<td>McGalliard et al ⁵⁴ ²</td>
<td>18</td>
<td>(2–12)</td>
<td>I</td>
<td>NR</td>
<td>11.0</td>
</tr>
<tr>
<td>Memmen et al ⁵⁴ ³</td>
<td>52</td>
<td>8.5 (1–17)</td>
<td>LCB</td>
<td>4.8</td>
<td>25.0</td>
</tr>
<tr>
<td>Naumann et al ⁵⁴ ⁴</td>
<td>68</td>
<td>6.3 (0.5–15.2)</td>
<td>LCB, C</td>
<td>6</td>
<td>51.1</td>
</tr>
<tr>
<td>Batioglu et al ⁵⁴ ⁵</td>
<td>41</td>
<td>3.2</td>
<td>I</td>
<td>NR</td>
<td>23.0</td>
</tr>
<tr>
<td>Shields et al ⁵⁴ ⁶</td>
<td>169</td>
<td>9.4</td>
<td>I</td>
<td>6 (4)</td>
<td>31.0</td>
</tr>
<tr>
<td>Current Study</td>
<td>51</td>
<td>8.7 (1–17)</td>
<td>I</td>
<td>6.7 (4.2)</td>
<td>30.4</td>
</tr>
</tbody>
</table>

†Largest basal diameter in millimeters (clock hours of iris involvement).
‡% mixed or epithelioid cell on histology.
NR = not recorded.

Of the 27 patients who were initially observed, one was lost to follow up. Three remained unchanged (average follow up period 6.75 years), 19 had documented growth, one had a recurrent hyphaema, and three developed raised intraocular pressure. Twenty two underwent interval local tumour resection and one patient, who had initially refused local resection, was enucleated. Of the cases in whom local resection was attempted, in all except one, macroscopic clearance of tumour was achieved. The latter patient had the eye enucleated within a few days of the initial surgery.

Of the 44 patient who underwent local resection, doubt was raised by pathological examination regarding clearance at the iris root/angle or ciliary body margin in eight cases (this includes the three cases which were macroscopically incomplete). The mean follow up period for these cases was 10.4 years.

HISTOPATHOLOGY CLASSIFICATION

Histopathological information was available for 46 cases. Thirty two were spindle cell melanomas, three of which were predominantly spindle A and 18 predominantly spindle B (the other 11 were reported as spindle A and B). Thirteen were mixed spindle and epithelioid cells and one was predominantly epithelioid. Univariate statistical analysis indicated that the variables predicting a less favourable histology (that is, epithelioid cell component) included: (i) documented rapid (<3 years) growth (p= 0.002), (ii) prominent tumour vasculature (p=0.004), and (iii) non-uniform lesion pigmentation (p=0.001). Each of these factors was given a score of +1 and patients were allocated into groups according to the number of factors present. A significant association was found between the presence of two or more of these clinical features and epithelioid cells on histology (p=0.001), although one mixed cell tumour had none of these features. In this series, pupil distortion, ectropion uveae, sector cataract, and anterior chamber angle involvement were not significantly associated with an epithelioid cell component (p>0.05). There was a strong association between patients who had anterior chamber angle involvement clinically and invasion of the anterior ciliary body histopathologically (n=33, p<0.001).
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Table 4  Postoperative complications of patients undergoing local resection

<table>
<thead>
<tr>
<th>Complication</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged corneal endothelial decompensation</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Wound fistula with chronic aqueous leak</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Lens subluxation</td>
<td>7</td>
<td>15.9</td>
</tr>
<tr>
<td>Complicated cataract</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Troublesome postoperative photophobia</td>
<td>11</td>
<td>25.0</td>
</tr>
</tbody>
</table>

12.5% with pupil reconstructed v 47.6% with pupil not reconstructed; n=8 and n=21 respectively.

CLINICAL FOLLOW UP
Fifty seven patients who had undergone surgical treatment (local excision or enucleation) and three patients with suspicious lesions were followed up. The mean follow up duration was 8.7 years (range 1–17 years). Four surgically managed patients have been lost to follow up since the surgery at the time of writing (mean follow up duration 5.2 years), the remainder are under periodic review. No patients have died from metastatic melanoma. The patient with spindle A melanoma who had an initial biopsy and was then observed, remains well and without ocular complications with 16 years of follow up. The patient with extraocular extension who underwent primary enucleation has been followed for 8 years and remains disease free. Clinically evident residual tumour (defined as any clinical evidence of tumour within the first 28 postoperative days) was observed in three patients. All these patients had bulky tumours with extensive angle involvement (4–5 clock hours). One of these patients died 2 years later from unrelated disease while the other two remain well and free of metastatic disease 9 and 12 years later. Local tumour recurrence was observed in four patients, two of these patients had tumour cells encroaching close to margins in the region of the angle or ciliary body. One had epitheloid, two mixed cell, and one spindle B on histopathology. The mean duration between initial surgery and recurrence was 3.25 years (range 1–7 years). Two patients with recurrence underwent subsequent enucleation and have remained disease free since, the other two remain under observation. In one of these patients a peripheral iris biopsy showed spindle B melanoma at a site remote from the site of the original tumour mass. The other patient clinically displays multiple areas of recurrence of an epitheliod tumour in an only eye and has elected to be observed. Both of these patients remain well and free of metastatic disease to date—12 and 7 years respectively after diagnosis of the recurrence.

POSTOPERATIVE VISUAL OUTCOME
Of 42 patients who had undergone local resection (excluding those patients enucleated within a few days of the procedure), 33 (78.6%) had best corrected visual acuity within the first postoperative year of 6/12 and the remainder were 6/36 or better. The proportion with a best corrected visual acuity of 6/12 or better declined to 28 (66.7%) at more than 1 year postoperatively. In all patients the cause of the visual deterioration was cataract progression, which could be treated surgically. Postoperative visual acuity compared with the preoperative vision improved in two (4.8%), remained stable in 12 (28.6%), and declined to some degree in 28 (66.7%) patients.

INTRAOPERATIVE AND POSTOPERATIVE COMPLICATIONS
Intraoperatively there were three cases of vitreous loss associated with more extensive iridocyclotrabeculectomy excisions which were successfully managed by conventional surgical techniques. No cases of intraoperative vitreous haemorrhage were encountered. The postoperative complications experienced are described in Table 4. A wound fistula formed in one case and was treated with a scleral graft. Prolonged endothelial compensation gradually resolved postoperatively over a period of 6 months in another patient. The most common reversible complication was cataract progression in 15.9%. Three patients had postoperative glaucoma and in one of these patients, resulted in enucleation 7.5 years after the initial surgical procedure. Troublesome postoperative glare was reported by 25% of patients. In the majority, the symptom could be adequately relieved by the use of tinted glasses. Since early 1992, pupil reconstruction at the time of resection has been attempted. One of the 10 patients who underwent pupil reconstruction reported troublesome postoperative glare as opposed to 10 (31.2%) of those patients who were not reconstructed (p=0.04). The melanoma was situated superiorly in 10% of the cases that underwent pupil reconstruction and 20% in those who did not.

Discussion
The present series includes patients managed by one surgeon over a period during which surgery on anterior segment lesions has seen significant evolution. Most notable are the changes in microsurgical techniques and instrumentation. For these reasons, the results of this study may not be representative of what can now be regularly achieved. Nevertheless, these results suggest that local resection has the advantage of providing a histological diagnosis, few complications with preservation of the globe, and a good level of long term visual function with no demonstrated increased mortality. Local radiotherapy and charged particle irradiation have recently received attention for the conservative management of iris melanomas.17–20 The complications of ocular radiotherapy are well known and it is recognised that many of these have a considerably delayed onset, often years after the initial treatment. However, few studies have reported on the long term outcome of these therapies for iris melanoma.17–20 Further series comparing resection with local radiotherapy treatments with long term follow up are still required to clarify the relative indications for these modalities.

DIAGNOSTIC FEATURES
The decision to treat or observe a suspect iris melanoma is currently based on the clinical
features. In this series no simulating lesions were excised and there was a low excision rate for spindle A melanomas demonstrating a high degree of diagnostic accuracy for the criteria used.

Distinguishing features associated with a less favourable prognosis is important for management decisions, as such patients may warrant earlier intervention. A number of studies have demonstrated that one feature associated with a less favourable outcome and higher risk of metastasis for uveal melanoma is the histology, especially the presence of epithelioid cells. In this study, we identified three features which were associated with an epithelioid component histologically: (i) rapid growth, (ii) prominent tumour vessels, (iii) heterogeneous pigmentation. Taken in association with other features, these factors may have an important role in enhancing diagnostic accuracy for more aggressive iris melanomas. However, absence of these features does not exclude the possibility of a more malignant phenotype.

Documented growth of suspicious lesions was present in the majority of excised cases presented here and represents an important diagnostic feature. However, previous studies have reported that even naevi may display slow growth which does not necessarily indicate malignancy. We examined a subset of tumours which displayed a more rapid growth curve (<3 years) and found a significant association with an epithelioid/mixed cell histology. This observation is supported by studies of the pathogenesis of melanoma where slow growth of benign or precursor lesions occurs, being replaced by entry into an accelerated growth phase associated with malignant progression. These findings highlight the need for regular lifelong review of these lesions with careful biometry and documentation of the relation of the tumour to surrounding landmarks (especially the angle structures) to enable timely detection and management of melanomas displaying malignant change.

The other features identified, including prominent tumour vasculature and variable lesion pigmentation, have received less attention in the literature. The requirement for the development of an intrinsic vasculature to supply an increasing tumour mass is well recognised. These vessels often have an disorganised structure and usually lack barrier function; properties which may be useful diagnostically in distinguishing new vessels in the context of malignancy from those seen in benign conditions. Regarding pigmentation, iris melanoma pigmentation may range from highly pigmented to largely amelanotic, although some residual pigmentation is usually present. We looked at the variability of pigmentation within a lesion and found that heterogeneity of pigmentation more often was associated with a malignant histology compared with a uniform pigmentation. This perhaps reflects increasing cellular heterogeneity associated with malignant progression resulting in clones of tumour cells with divergent phenotypic features associated with the variable accumulation of genetic errors. New angiographic techniques with improved transmission through melanin such as indocyanine green combined with confocal image analysis may have potential implications for more precise evaluation of these features in clinical practice.

SURGICAL MANAGEMENT

Three patients had residual disease after local resection. Residual tumour was invariably observed in association with lesions toward the upper limit of resection (4–5 clock hours). The use of a larger lamellar flap involving splitting the corneal stroma allows direct visualisation of the tumour through the deep cornea and we believe that this has been a significant advance in enhancing complete removal of the tumour. To date, the presence of residual disease has been managed by prompt enucleation without an incidence of metastatic disease. However, with improved microsurgical and radiotherapy techniques, small areas of tumour residuum may in future be amenable to further attempts at localised therapy which preserves the globe.

Recurrent tumour was observed in four patients. As noted in other series of uveal melanoma, most recurrences occurred within the first 3 years after treatment, although one case occurred 7 years later, indicating that prolonged postoperative follow up of these patients is necessary. In two of the cases, the patients had multiple iris naevi and second tumours developed at sites quite distant from the original resection site and it could be argued whether these cases represent recurrent disease or multiple primary tumours. In the other cases, both had subtle recurrent disease in the adjacent angle region associated with a rise in the intraocular pressure. Both these cases involved an epithelioid component on histology and one had tumour cells reaching the ciliary body margin of the resection. It has been reported previously that raised intraocular pressure in the context of iris melanoma is often from infiltration of the angle by tumour cells. These cases suggest that in following patients after treatment, a rise in the intraocular pressure should also be viewed with a high level of suspicion and careful consideration given to the possibility of tumour recurrence. Adjuvant radiotherapy has an established role for the management of microscopic residual disease in a variety of malignancies. Risk factors for recurrence of iris melanoma have not been determined. With the small number of recurrences involved in the present study, we were unable to identify a subgroup who may benefit from adjuvant therapy. More aggressive histology, extensive tumour cell seeding, raised intraocular pressure, or tumour cells to the margin of the resection may be significant factors and await further evaluation through a larger patient series.

Real difficulty exists in determining the extent of melanoma invasion of the ciliary body, even with state of the art imaging techniques. Although there may be doubt raised as to tumour clearance of surgical...
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agreement with other studies, the use of generous superficial lamellar dissections hinging the flap in clear cornea may contribute towards decreased vitreous loss by reducing distortion and pressure on the globe during dissection. The importance of well controlled hypotensive anaesthesia, prophylactic vitrectomy in selected cases, avoidance of diathermy around the ciliary body (which tends to distort and pull tissues), and employing blunt dissection to the ciliary body component of the tumour may be other factors involved.

The major postoperative complications we experienced have been postoperative glare, cataract progression, and postoperative glaucoma. We did not encounter clinically significant macular oedema in this series and this may be correlated with the reduced incidence of disturbance to the vitreous. Milder cases, however, could not be excluded as fluorescein angiography was not routinely performed. In a number of cases, cataract has been successfully removed with excellent visual rehabilitation. Troublesome postoperative glare symptoms were reported by just over a quarter of our patients. In the past 10 years, pupil reconstruction has been performed in suitable cases (usually less than 3–4 clock hours resected) and although the numbers are small, the results here suggest that this procedure has a useful role, not only by enhancing cosmesis but also in reducing glare.

The authors wish to thank Dr Clare Fleming for facilitating follow up of cases with the NSW Cancer Registry records.