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Uveal Melanoma

J. Hungerford

UVEAL MALIGNANT melanoma is the commonest primary intraocular malignancy with an annual incidence averaging 7 per million [1]. Although congenital tumours have been reported, peak incidence is in late middle age: in one study there were 3 cases per million under 50 years and 21 per million per year over this age [2]. It is predominantly a tumour of fair-skinned Caucasians and is uncommon in Asians and Orientals and rare in Negroes. Sunlight exposure and other environmental stimuli are not known to be predisposing factors although iris melanomas are much more common inferiorly where this structure is not covered by the upper eyelid. A study from Denmark demonstrated no overall increase in the frequency of ocular melanomas during a period in which the incidence of its cutaneous counterpart had increased five or six times [3]. Host factors play a strong part in the development of this malignancy. Most choroidal melanomas are now thought to arise in pre-existing naevi. Naevi are present in up to 2% of eyes clinically and up to 6.5% at autopsy [4]. The chance of malignant change in a naevus has been estimated at less than 1 in 500 during a 10-year period [4]. Congenital ocular and oculodermal melanocytosis are strongly associated with uveal melanoma [5] and annual ophthalmoscopic screening is recommended. There have been reports of a familial incidence [6] and of bilateral uveal melanomas and some of these cases have been linked to the atypical mole syndrome (AMS) [7]. There is an increased incidence of uveal naevi in AMS [8] and unilateral and bilateral uveal melanomas have been seen to coexist with cutaneous melanomas in affected individuals [7]. AMS sufferers should be screened for ocular melanoma and *vice versa*.

There is no convincing evidence that local ocular treatments reduce the high mortality rate of uveal melanoma. Large tumour size is the single most important clinical indicator of a poor life prognosis [9]. Histology is also highly predictive and individuals with tumours containing epithelioid cells fare worse than those with pure spindle cell lesions [10, 11]. The clinical and histopathological features may not be independent predictors of outcome because it has been shown that large tumour volume is closely associated with epithelioid cell type [12]. Furthermore, although extrascleral extension is unfavourable, this too is closely associated with epithelioid cell tumours [13] and multivariate analysis does not demonstrate an independent adverse effect of extrascleral extension on survival rate [14]. Location within the uvea appears to have a prognostic significance which is independent of tumour size. Iris melanomas tend to have a good prognosis and, although this may be due in part to early detection because they are visible to the patient, a higher proportion of these lesions have a relatively benign spindle cell histology compared with their counterparts in the ciliary body and choroid [15]. Posterior choroidal melanomas may be detected when quite small because they disturb vision early during their development by encroachment on the macula. Furthermore, asymptomatic posterior melanomas are easy to see on routine ophthalmoscopy during a sight test. By contrast, ciliary body melanomas are difficult to visualise, tend not to disturb vision until late in their development when they produce a secondary retinal detachment and so are often very large when first detected. Although large size at diagnosis clearly contributes to the exceptionally poor prognosis associated with ciliary body melanomas, anterior location appears to have an adverse effect which is independent of size [11].

Diagnosis of large melanomas anywhere within the uveal tract poses few difficulties and, aided by non-invasive ancillary investigations and particularly by ultrasound, specialist ophthalmic oncologists can distinguish such tumours from simulating lesions with an accuracy approaching 98% [16, 17]. Cases of difficulty can usually be resolved by open biopsy of anterior tumours or fine needle aspiration biopsy of posterior lesions with relatively little risk of extrascleral spread or damage to the eye. Most typical melanomas are in excess of 3 millimetres in

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thickness and many are 12 millimetres thick or more when first detected. Like their cutaneous equivalents, such lesions are probably incurable, though the combined effects of lead time bias and the relatively long natural history of the disease may conspire to give the false impression that they are.

Small melanomas may be extremely difficult to diagnose and to distinguish from naevi. In the ciliary body, naevi are known to occur but are virtually impossible to visualise. It is in the iris and choroid that such lesions are best seen. Small flat naevi in both locations are almost always innocent. In the iris, patients can see their naevus and detect any change themselves so that regular re-evaluation is probably not necessary. In the choroid they cannot and annual review is ideal, though these lesions are so common that this policy may strain resources. Larger lesions with significant thickness are classified as suspicious naevi and warrant twice yearly observation with serial fundus photographs and ultrasounds looking for evidence of growth. Documented enlargement suggests malignant change but can occur in benign naevi. As with cutaneous naevi, these lesions are rarely seen in infancy and it is not surprising that they may grow for short a period around the time they are first detected. Continued growth however, particularly in thickness, is strongly suggestive of malignancy. Many suspicious choroidal naevi demonstrate additional features including orange lipofuscin pigment on their surface and accumulation of subretinal fluid. Whilst neither of these findings are absolute indicators of malignant change, they are also seen in many small melanomas. Most but not all melanocytic tumours less than 2 mm in thickness are benign whereas most but again not all lesions more than 2 mm thick are malignant.

It will be apparent that the boundary between the clinical diagnosis of large naevus and that of small melanoma is poorly defined. At present, there is no evidence that these lesions can be better delineated by ancillary investigations including fluorescein fundus angiography, ultrasound, the ^{32}P test, computed tomography and magnetic resonance imaging. Diagnostic excisional biopsy as performed for suspicious cutaneous lesions is feasible for iris tumours but has not gained popularity because the resultant defect is cosmetically noticeable and leads to photophobia and because the majority of biopsies are reported as benign. Excisional or incisional biopsy of small suspicious choroidal naevi is not technically possible and fine needle aspiration biopsy either fails or is inconclusive. The distinction requires skill and experience and forms a substantial part of the work of specialist ocular oncology clinics. Evidence is accumulating that the more suspicious features a naevus has the more likely it is that it will ultimately be reclassified as a melanoma [18].

In general, significant doubt usually exists about the true nature of most melanocytic lesions less than 3 mm thick. We can infer from experience of cutaneous melanomas that by the time a confident diagnosis of uveal melanoma can be made, it may be too late to achieve a cure. Until agents are available that can modify the metastatic process, the best chance for improving the outlook for patients with uveal melanoma lies in earlier detection. Hopes that radioimmunoscintigraphy could distinguish between benign and malignant lesions have not been fulfilled [19]. Until a more reliable method of making this important distinction is available it is now standard practice in London to treat peripheral suspicious naevi 2 mm or more in thickness and with orange pigment and subretinal fluid accumulation at presentation and without waiting for evidence of growth. It is recognised that some of these lesions may be naevi but their peripheral location means that there is minimal visual morbidity following therapy. Treatment of suspicious naevi around the posterior pole is followed by substantial visual loss and such lesions are still managed by observation. As soon as the diagnosis is certain active treatment is instituted.

Conservative therapy has superseded enucleation of the eye as the first-line treatment of all except the largest uveal melanomas and eyes with secondary glaucoma or massive extrascleral extension. Enucleation retains an important palliative role as the primary treatment of eyes with very extensive tumour involvement and for management of failure of conservative treatment or severe post-treatment side-effects. Unless there is intractable ocular pain or extrascleral spread, patients considered for enucleation should first undergo a metastatic evaluation. Unnecessary enucleation can thereby often be avoided in patients who are found to have unsuspected metastases, usually in the liver, skin or lungs. Postoperative radiotherapy to the orbit is recommended to reduce the incidence of recurrence in the socket when nodular extrascleral extension is present in an eye enucleated for melanoma [20]. Massive extrascleral spread in eyes with neglected melanomas may require orbital exenteration.

The conservative treatment method chosen depends on the size of the tumour, its location within the uveal tract and on the facilities available to the ocular oncologist. Most uveal melanomas are now treated in special centres which have been able to progressively refine the selection criteria for the various treatment methods on the basis of a large experience. There is wide variation in the cost of the different types of treatment and some degree of overlap between them in the selection process. Achieving the best possible rate of local tumour control takes precedence over all other factors and thereafter consideration is given first to preservation of vision and second to cost effectiveness.

In the U.K., patients are fortunate in having access to all treatment methods currently available. At present, in London, treatment technique is selected entirely on clinical criteria and not on the basis of availability.

Circumscribed anterior melanomas in the iris respond well to surgical excision though diffuse iris melanomas containing epithelioid cells are best managed by enucleation. Anterior melanomas confined to the iris and ciliary body and occupying less than one quadrant are also best excised. The ciliary body is difficult to examine and is a location in which ancillary tests are unhelpful. It is also an area where many pseudomelanomas are discovered. The opportunity which excision provides to obtain a tissue diagnosis is particularly advantageous for ciliary body tumours.

Small posterior melanomas 3 mm or less in thickness and located outside the vascular arcades of the macula may be treated by direct xenon arc photocoagulation [21] when it is considered that they are located too close to the optic disc to avoid loss of vision from radiation-related ischaemic optic neuropathy. By far the majority of posterior uveal melanomas, however, are treated by radiotherapy either with episcleral radioactive plaques or with accelerated protons. Radiotherapy methods depend on achieving a high dose of 60 to 100 Gy within the tumour whilst at the same time keeping the dose to the retina, choroid and when possible to the optic nerve below the 50 Gy or so tolerated by these structures. Radioactive plaques achieve these aims because their radiation is attenuated rapidly with increasing distance from the source. The attenuation depends on the inverse square law and the benefit is progressively lost with increasing tumour thickness. In practice, the size of melanoma

which can be treated by plaque without serious side-effects depends on the energy of the source and on the location of the tumour [22]. Posterior melanomas up to 5 mm in thickness in all locations can be treated with ruthenium-106/rhodium-106 plaques emitting β rays [23]. Posterior to the equator, melanomas up to 8 mm in thickness and anterior to it up to 10 mm thick can be treated with iodine-125 plaques emitting X-rays [24]. These modern plaques are shielded on their external surface and produce no significant side-effects on the ocular adnexa. Proton therapy relies on the dose distribution advantages of positively charged particles [24]. The pencil beam is finely collimated and directed to the ocular tumour with the aid of surgically applied tantalum marker clips. The Bragg peak of protons means that the entry dose is reduced and that the exit dose is zero. Proton therapy is expensive and the absolute indications for it are currently confined to posterior melanomas which are too large or too close to the optic disc to treat by plaque. Proton therapy may preserve central vision better than plaques when used to treat melanomas close to the macula. Eyes containing melanomas with a volume greater than 1.5 cc are no longer selected for proton therapy in London because most have been lost from neovasular glaucoma. These eyes are enucleated. The surface-sparing advantages of the Bragg peak are progressively lost with increasing modulation of the beam to treat larger and larger tumours, and with anterior location. Eyelid damage is unacceptable when protons are used to treat large anterior melanomas. Plaque therapy or excision are employed whenever possible for such tumours and when not, the eye is enucleated. By careful case selection, more than 90% of eyes can be retained after plaque or proton radiotherapy, most with useful acuity or field of vision. Modern surgical techniques allow some larger posterior melanomas to be resected [26]. The technique is particularly applicable to tumours which present with an extensive serous retinal detachment. Large bullous detachments are slow to resolve after radiation treatments and this predisposes to secondary neovascular glaucoma. Surgical resection often allows rapid retinal reattachment and thereby a better outcome. The results of resection are better for tumours situated behind the ora serrata than for cilio-choroidal melanomas which straddle this structure. Temporal tumours are technically the easiest to resect but the visual results are better following excision of nasally located lesions. Unfortunately, successful surgical resection of posterior uveal melanomas requires profound hypotensive anaesthesia. Enthusiasm for this technically attractive procedure has to be tempered with an awareness of the risks to elderly patients. In London, only patients under 50 with no cardiac history are selected for this treatment when the contralateral eye is healthy. If resection is considered to be the only way of preserving vision in a one-eyed patient over 50, the risks of the operation are explained.

Some centres recommend regular re-evaluation for evidence of metastases but there is no evidence of improved outcome following early detection and treatment of asymtomatic dissemination to justify the upset to the patient and the expense of this approach.

Radical treatment by enucleation was formerly recommended for most uveal melanomas but no study has ever shown removal of the eye to be superior to conservative therapy in preventing dissemination. Consequently, treatments which aim to preserve the eye are now recommended wherever possible. This policy is less controversial than it was but still has its opponents. To date, all completed studies comparing one form of treatment with another have been retrospective. Careful investigators have been at great pains to match the two arms of their studies for the known clinical risk factors such as tumour size and location. Purists, however, take the view that the only reliable way to avoid selection bias is to conduct a prospective randomised trial. With this in mind, the Collaborative Ocular Melanoma Study (COMS) has been designed and is currently under way as a multicentre investigation funded by the National Institutes of Health. A main aim of COMS is to compare radioactive scleral plaque therapy for posterior uveal melanomas with enucleation. So far, COMS has demonstrated no significant difference between the two treatment arms. If the trial confirms that patients treated by plaque therapy have a survival rate as good as those who are enucleated, we must not assume this means that radiation is as good as removal of the eye in eliminating the primary tumour. Most of the tumours randomised in COMS are of medium size. The maximum size of uveal melanoma which is potentially cureable is not known but many of the studied tumours may be too large to cure. Without prejudging the result of COMS, it could well confirm that it is perfectly legitimate to treat medium-sized melanomas by plaque therapy because local tumour control is good and morbidity low whilst survival is no worse than that achieved by enucleation. However, we cannot extrapolate from the results of this COMS investigation and assume that the same results would apply to very early lesions which might be potentially cureable. We know that plaque therapy has a small but significant failure rate. Whilst this may be due in part to targetting error there remains a very real possibility that the treatment does not always kill the primary tumour. Either way, plaque treatment failures could be more serious for patients with very small lesions who might otherwise be cured by enucleation. It would be difficult to carry out a separate randomisation to enucleation or plaque therapy for individuals with very small lesions because this group would certainly contain some naevi [27]. We would learn that this was so in the enucleation arm and this would clearly be upsetting. We would not know which plaque-treated lesions were naevi because we would not have a tissue diagnosis for patients in this arm. This dilemma may be resolved by a subsidiary study randomising very small lesions to no treatment or to plaque therapy, though the natural history of melanoma is such that we will wait a very long time for an answer.

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Papers

Suppression of Serum Insulin-like Growth Factor-1 Levels in Breast Cancer Patients during Adjuvant Tamoxifen Therapy

Andreas Friedl, V. Craig Jordan and Michael Pollak

Serial IGF-1 levels in patients prior to and during adjuvant tamoxifen (TAM) treatment were followed in a retrospective study. Serum IGF-1 levels were determined by radioimmunoassay in 19 patients taking TAM and 19 controls, matched for age, body weight and other treatments. IGF-1 levels at 2 years were significantly lower in TAM patients ($P \leq 0.05$) compared to control patients. We observed a significant mean drop from pre-treatment to treatment IGF-1 levels by 19.9% in the TAM group ($P \leq 0.005$), but also noted a mean 11.4% decline in the control group ($P \leq 0.025$). A subgroup analysis suggested that premenopausal were relatively resistant to the IGF-1 lowering effects of TAM as compared to postmenopausal women.
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INTRODUCTION

RESPONSE to tamoxifen (TAM) in advanced breast cancer [1] and prolongation of disease-free survival in the adjuvant setting [2, 3] is largely restricted to patients with oestrogen receptor (ER)-positive primary tumours. However, a minority of approximately 13% of patients with ER-negative tumours also respond to TAM [1]. Additionally there are some breast cancer patients who experience a benefit from TAM after they have failed ablative hormonal treatment [4] or other endocrine manipulation [5]. The recently published overview analysis by the "Early Breast Cancer Trialists Collaborative Group", which includes 30 000 breast cancer patients treated with TAM provides the strongest evidence in favour of a TAM effect on ER-negative tumours [6]. The report concludes that TAM reduces the incidence of recurrences in the "ER-poor" subgroup (as defined by ER negative or < 10 fmol/mg protein) by 13%. An 11% reduction in mortality is seen in the same subgroup. Both results are statistically significant.

It appears that the classical concept of antioestrogen action, which is based on competitive inhibition of oestrogen binding to