

# THE LIVERPOOL OCULAR ONCOLOGY CENTRE

A Guide for Practitioners

Bertil Damato



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# PREFACE

I have written this guide so that you at the referring hospital and we at the ocular oncology service in Liverpool can work together as efficiently as possible to ensure that our mutual patients receive the best possible care.

This guide should not be regarded as a set of 'standards of care' or 'clinical guidelines'. It is based on my personal experience in ocular oncology and a review of the literature. It would have been ideal if all the suggestions and recommendations were based on evidence from randomised prospective studies. These are few and far between, however, because of the rarity of patients for whom there is equipoise when there is a choice of treatments and because of logistical difficulties preventing multi-centre studies. Much of the guide might seem quite obvious and perhaps superfluous but has nevertheless been included for the benefit of any trainees, non-specialists and lay persons reading this text.

This guide focuses on protocols, because ocular tumours and their treatment are already described quite adequately in several books and chapters. Only adult tumours are covered, because our centre does not specialise in paediatric ocular oncology. References are kept to a minimum, because it is so easy to search the literature on the Internet. For the sake of convenience, these are listed in the last chapter.

I wish to thank Sister Jane Humphreys (Specialist Nurse), Mrs Julie Sudlow (Secretary), Mrs Sharon Cook (Health Psychologist), Miss Lisa Dixon (Ophthalmic Photographer), Miss Amber Tierney (Compliance Officer), Mr Gary Cheetham (Data Manager), Sister Jean Hannah (Ophthalmic Nurse), Dr Nikolaos Trichopoulos (Ocular Oncology Fellow) and Dr Werner Wackernagel (Visiting Ocular Oncology Fellow) for their assistance. The publication of this guide has been financed by donations from our ocular oncology patients, through the Eye Tumour Research Fund.

Ocular oncology is developing rapidly and so are our protocols. I therefore anticipate that this guide will be updated regularly. Your comments or suggestions would be most welcome.



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# DETECTION OF OCULAR TUMOURS

Many asymptomatic tumours are detected as a result of routine screening, for example, performing bilateral ophthalmoscopy when the patient has presented for new spectacles.(Damato 2001a) However, it is not uncommon for patients to present with a symptomatic choroidal tumour soon after having an eye examination, suggesting perhaps that the ophthalmoscopy was limited to optic disc and macula. A significant proportion of patients with uveal melanoma report that their tumour was not detected when they first presented on account of symptoms. We have found statistically that in comparison with symptomatic patients whose tumour was immediately detected, such individuals experience longer delays in obtaining treatment and are also more likely to lose vision and the eye.

In the UK, there is no consensus as to whether both pupils should be dilated in all patients or only if there are any specific indications. It is beyond the scope of these guidelines to comment on what is acceptable in routine general ophthalmic practice.

For situations where mydriasis is performed selectively, I have devised the mnemonic, MELANOMA, to help remember the symptoms and external signs that might indicate the presence of a uveal melanoma. Of course, some of these features are not specific to melanoma, or indeed to any tumour, and can be caused by other pathology.

## The features suggestive of uveal melanoma, include:

- M** Melanoma visible externally, as extraocular extension, an iris tumour, or iris heterochromia.
- E** Eccentric visual phenomena, such as field loss and photopsia, caused by a tumour or secondary retinal detachment.
- L** Lens abnormalities such as astigmatism and cataract, caused by a ciliary body tumour.
- A** Afferent pupillary defect, caused by tumour or retinal detachment.
- N** No optical correction, because of blurring or metamorphopsia from macular oedema, retinal detachment or tumour.
- O** Ocular hypertension from rubeosis iridis or tumour cells or macrophages in angle.
- M** Melanosis oculi (naevus of Ota).
- A** Asymmetrical episcleral vessels, indicating a ciliary body tumour.



Fig.1.1 Sentinel vessels

# OCULAR EXAMINATION AT LOOC

This chapter describes how patients are assessed at our Ocular Oncology Centre in Liverpool.

## HISTORY TAKING

### Initial Assessment

**For several years we have been auditing the mode of presentation of ocular tumours and we therefore record:**

- The nature of any symptoms, together with the date of onset
- Date of initial presentation, the type of practitioner and the outcome of that consultation
- The date of the subsequent assessment, the practitioner involved and the outcome
- Any change in ocular status during the referral process

**Using a proforma in the casenotes, we also obtain a full history, including:**

- Systematic enquiry
- Past ocular and systemic history
- Family history of ocular and systemic disease
- Topical and systemic medications
- Present and past history regarding smoking, alcohol and other habits.
- Allergies
- Social and occupational status

The history can sometimes provide diagnostic clues, for example, if the patient has been a heavy smoker for many years or if a previous mastectomy has been performed. While such information might suggest the source of an intraocular metastasis, it should not be relied upon to distinguish between a metastasis and other types of tumour, such as melanoma and haemangioma. This is because dual pathology is not uncommon.

The history also provides an understanding of the patient's visual needs, which may help in the selection of the most appropriate form of treatment.

The duration of the visual loss can have prognostic significance, for example, in patients with choroidal haemangioma in whom visual loss is irreversible if long-standing.

## VISUAL ACUITY

Since January 2005, we have measured the visual acuity using a LogMAR chart, which overcomes the limitations of the Snellen test. Initially, we recorded the Snellen equivalent vision but have recently transferred to a numerical score, to facilitate statistical analyses.

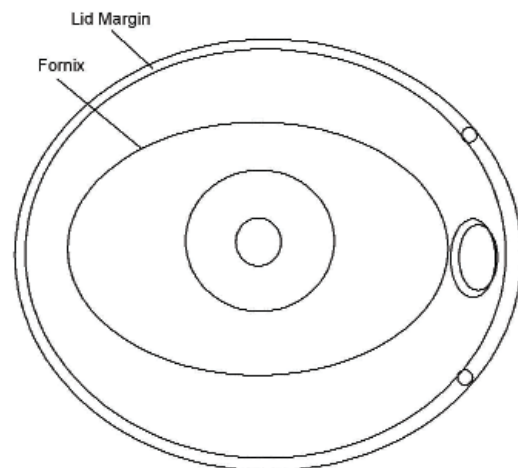
If central vision is lost, the eccentric visual acuity is measured using the optotype and, if necessary, Finger Counting, before checking for Hand Movements vision.

The visual acuity is measured with spectacles and with pinhole if the visual acuity is worse than 6/9.

## CONJUNCTIVAL EXAMINATION

When the patient has a conjunctival tumour, we examine the entire conjunctiva. We assess the superior fornix by gently pinching the eyelid skin and pulling the eyelid away from the globe, examining the fornix with a binocular indirect ophthalmoscope and 20D lens. Palpation of the pre-auricular, cervical and submandibular areas are performed routinely, to detect any lymph node enlargement.

We specifically assess the primary tumour, document any secondary effect, identify any predisposing factors and recognise any concurrent disease.



**Fig.2-1. External eye and anterior segment diagram**

### Primary Extraocular Tumour

**A primary conjunctival or corneal tumour is described according to:**

- Most likely site of origin (i.e. conjunctiva, cornea, intraocular structures, eyelid)
- Quadrant (i.e. superior, supero-nasal, nasal, etc).
- Circumferential spread, in clock minutes in a clockwise direction (e.g. 5 to 30 or 55 to 5). This is easier than using degrees and more precise than clock hours. Circumferential spread can be described separately for any tumour at limbus, bulbar conjunctiva, palpebral conjunctiva, and lid margin
- Posterior extent (e.g. cornea, limbus, bulbar conjunctiva, fornix, palpebral conjunctiva)
- Anterior extent (e.g. cornea, limbus, bulbar conjunctiva, fornix, palpebral conjunctiva, lid margin, skin)
- Consistency (i.e. solid, cystic, multicystic).
- Shape (i.e. flat, dome, unifocal-multinodular, multifocal)
- Margins (i.e. diffuse, discrete)
- Colour (i.e. pink, white, tan, etc)
- Vascularity (present or absent)
- Seeding (i.e. across conjunctiva, into cornea, etc).
- Deep invasion (i.e. conjunctival stroma, sclera, and intraocularly)
- Extraocular spread (i.e. pre-auricular, sub-mandibular nodes, etc)
- Longitudinal and transverse basal dimensions, using the measure on the slit-lamp

### Secondary Effects of Extraocular Tumour

**These include features such as:**

- Feeder vessels
- Infection
- Haemorrhage

### Predisposing Conditions for Extraocular Malignant Tumours

**These include conditions such as:**

- Primary acquired melanosis
- Eyelid sebaceous gland carcinoma
- Actinic keratosis

### Concurrent Disease

**Abnormalities that may be relevant to the treatment of the ocular tumour include:**

- Keratoconjunctivitis sicca
- Marginal keratitis
- Ingrowing lashes

### ANTERIOR SEGMENT EXAMINATION

**An anterior segment tumour is described according to:**

- Most likely site of origin (i.e. iris, ciliary body, choroid)
- Quadrant (i.e. superior, supero-nasal, nasal, etc)
- Circumferential spread, ideally in clock minutes in a clockwise direction (e.g. 5 to 30 or 55 to 5)
- Posterior extent (e.g. choroid, pars plana, pars plicata, pupil margin, iris surface)
- Anterior extent (e.g. iris surface, angle, cornea)
- Longitudinal and transverse basal dimensions, using the measure on the slit-lamp. (See below for ultrasonography)
- Consistency (i.e. solid, cystic, multicystic)
- Shape (i.e. flat, dome, multinodular)
- Margins (i.e. diffuse, discrete)
- Colour (i.e. pink, white, tan, etc)
- Vascularity (present or absent)
- Seeding (i.e. across iris or into angle)
- Angle involvement (i.e. in clock minutes). With melanoma, it can be difficult to distinguish tumour from melanomacrophages clinically
- Extraocular spread (i.e. absent, nodular, diffuse)

### Secondary Effects of Intraocular Anterior Tumour

**These include:**

- Glaucoma
- Lens abnormality (e.g. cataract, deformity, subluxation)
- Dilated episcleral vessels, in the presence of ciliary body involvement
- Iris cyst formation
- Ectropion uveae
- Pupillary peaking
- Hyphema
- Band keratopathy

### Predisposing Conditions for Intraocular Tumours

#### These include:

- Ocular or oculodermal melanocytosis
- Sturge-Weber syndrome and other vascular malformations
- Corneal scar, if the patient has an anterior chamber cyst

### POSTERIOR SEGMENT EXAMINATION

As with anterior segment and conjunctival tumours, it is necessary to describe the primary tumour, any secondary effects and any predisposing factors.

#### Primary Tumour

To describe a posterior segment tumour properly, as many of the following features as possible should be noted:

- Tissue of origin (e.g. choroid, retina, RPE)
- Shape (e.g. dome, collar-stud)
- Margins (i.e. discrete, diffuse)
- Tissue colour (e.g. grey, pink, white, etc).
- Vascularity (e.g. vascular, avascular)
- Quadrant (e.g. superotemporal, superior, superonasal, etc)
- Posterior extent, including distances to optic disc margin and fovea (i.e. in disc diameters)
- Anterior extent (i.e. post-equatorial, pre-equatorial, pars plana, pars plicata, etc)
- Circumferential involvement of disc and ciliary body (e.g. in clock minutes)
- Internal spread (e.g. sub-retinal space, retina, vitreous)

#### Secondary Effects

The presence of any secondary effects should be recorded, which include:

- RPE changes overlying tumour (i.e. drusen, orange pigment, disciform)
- RPE changes adjacent to tumour (i.e. marginal atrophy, cobblestone degeneration, 'comet's tail' or 'peacock tail' atrophy)
- Exudative retinal detachment (i.e. over tumour surface, inferior retina, with an estimate of the percentage of retina detached)
- Haemorrhage (i.e. subretinal, vitreous, etc)
- Cataract
- Glaucoma

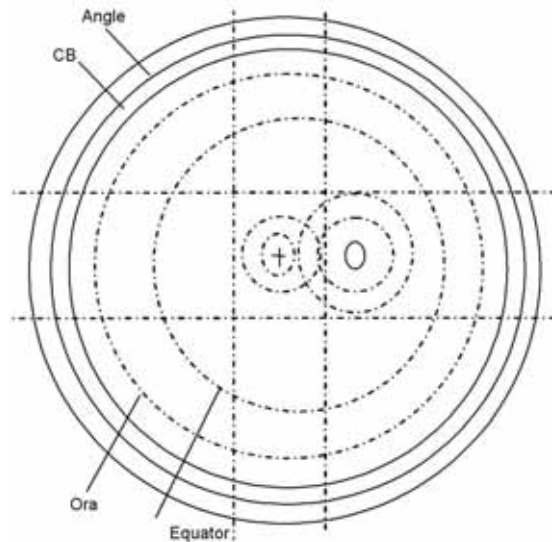


Fig.2-2. Fundus diagram

### Predisposing Conditions

#### These may include:

- Ocular melanocytosis
- Melanocytoma
- Diffuse choroidal hemangioma

### THREE-MIRROR EXAMINATION

Some routinely perform three-mirror examination on all patients. If done selectively, the indications are to:

- Identify the cause of raised intraocular pressure
- Determine whether a lesion behind the iris is solid or cystic
- Find a small, retinal angioma
- Determine the anterior extent of a pre-equatorial tumour
- Measure the circumferential extent of ciliary body or angle involvement by a tumour, aligning in turn each lateral tumour margin with the centre of the mirror

## TRANSILLUMINATION

### Transillumination can be:

- Trans-pupillary, placing the illuminator on the cornea. Care is taken not to over-estimate posterior extension because of a shadow cast by a thick tumour
- Trans-ocular, with a right-angled transilluminator on the globe directly opposite to the tumour. This is less convenient than trans-pupillary transillumination, but slightly more accurate
- Trans-scleral, with the light source on the sclera over the tumour. This only determines whether or not the tumour transmits light

Not all pigmented tumours are melanoma and, conversely, not all melanomas are pigmented.

## COLOUR PHOTOGRAPHY

### Colour photography is useful for:

- Documenting the tumour size and its distances from optic disc and fovea (e.g. in disc diameters). This information is particularly useful when the tumour shows diffuse spread that is not adequately demonstrated with ultrasonography
- Documenting the circumferential location of the tumour with respect to fovea. This is useful when preparing a 3-D model of the eye for planning radiotherapy

Colour photography helps to determine whether or not the tumour is growing, for example, if differentiating naevus from melanoma or to detect marginal tumour recurrence after conservative therapy.

The image obtained with the binocular indirect ophthalmoscope is compared with a colour transparency, which is looked at using a hand-held, battery-powered viewer held near the patient's eye. The relationship between tumour margins and adjacent retinal vessels is noted, taking into consideration any variation in magnification and illumination.

There is a trend towards digital imaging and wide-angle photography. We use a digital fundus camera in selected cases, but are hoping to stop using film soon.



We are awaiting delivery of a wide-angle fundus camera, purchased using our Eye Tumour Research Fund.

When photographing extraocular tumours, the angle of illumination is adjusted to highlight any surface features of the tumour. When an iris lesion is photographed, care is taken to avoid corneal reflections over the lesion.

All patients are asked to sign a consent form for the use of their images for teaching, research and audit purposes and for publication in journals and electronically. If the face is photographed so that the patient is identifiable, special consent is obtained.

## FLUORESCEIN ANGIOGRAPHY

### Tumour fluorescence is related to:

- Fluorescein concentration in the tumour stroma
- Hyperfluorescent RPE abnormalities, such as drusen, RPE detachments, choroidal new vessels and serous retinal detachment
- Intervening pigments, which include (a) melanin in the tumour and RPE; (b) haemoglobin in any haemorrhages; and (c) lipofuscin (i.e. 'orange pigment')
- Reflections from white tissue, such as exposed sclera
- Autofluorescence, which occurs with optic disc drusen

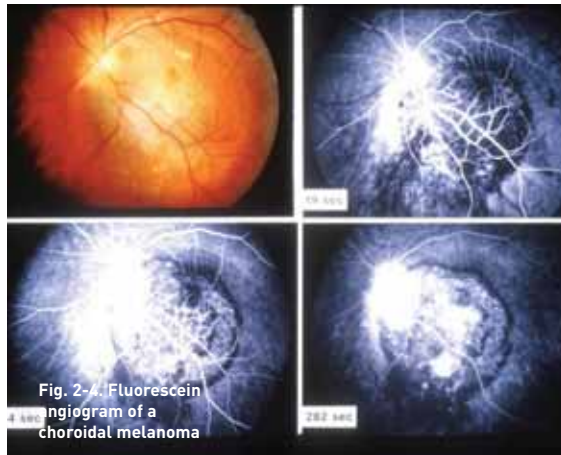


Fig. 2-4. Fluorescein angiogram of a choroidal melanoma

The implication of these principles is that fluorescence does not indicate whether a lesion is benign or malignant. (Damato & Foulds 1990) Hypofluorescence after phototherapy or radiotherapy of a choroidal melanoma does not necessarily mean that the tumour is destroyed. We perform fluorescein angiography only when investigating retinal vascular tumours and ocular neovascular complications.

### INDOCYANINE GREEN ANGIOGRAPHY (ICG)

The principles of fluorescein angiography apply to indocyanine green angiography (ICG), except that the infra-red light is not absorbed by melanin and haemoglobin to the same extent as fluorescein, so that changes in the RPE and retina are less conspicuous.

Confocal indocyanine green angiography has identified complex microcirculation patterns in choroidal melanocytic tumours. We may start performing this examination in patients with small, melanocytic choroidal tumours if studies ever show that microcirculation patterns predict tumour growth and metastatic disease.

Although choroidal haemangiomas show typical features on ICG angiography this investigation is not usually necessary because the ophthalmoscopic appearances are so characteristic.

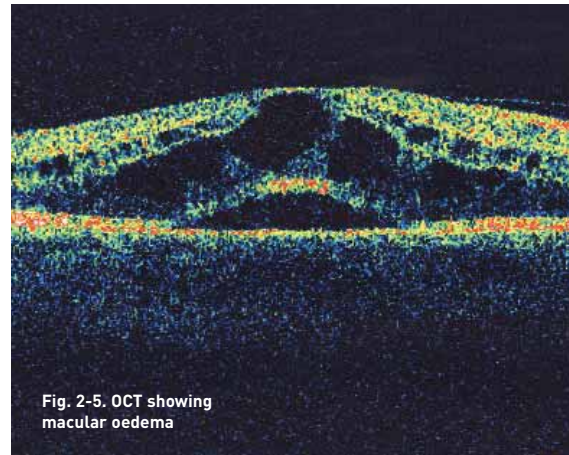


Fig. 2-5. OCT showing macular oedema

### OPTICAL COHERENCE TOMOGRAPHY (OCT)

In patients with a uveal tumour, optical coherence tomography (OCT) is most useful for demonstrating maculopathy secondary to the tumour or its treatment and assessing the response of such maculopathy to therapy. We do not use OCT as a diagnostic tool.

### ULTRASONOGRAPHY

**Our indications for ultrasonography (also known as echography) are to:**

- Detect an intraocular tumour when the media are opaque, for example, in the presence of vitreous haemorrhage or cataract
- Detect posterior extraocular tumour extension.
- Define the shape of the tumour. A collar-stud shape is almost pathognomonic for uveal melanoma
- Measure tumour dimensions and distances to optic disc and lens. This is useful for treatment selection and planning
- Demonstrate internal acoustic reflectivity, which may suggest a particular diagnosis

**The types of ultrasonography include:**

- A-scan ultrasonography, with a stationary transducer, which produces a parallel, one-dimensional beam. Standardised ultrasonography uses an 8 MHz probe, calibrated with a model eye
- B-scan ultrasonography, performed with an oscillating transducer, which produces a two-dimensional beam focused near the retina

- High-frequency ultrasonography, which defines structures anterior to the ora serrata
- Doppler ultrasonography, which demonstrates blood flow
- Three-dimensional imaging can enhance tumour volume measurements

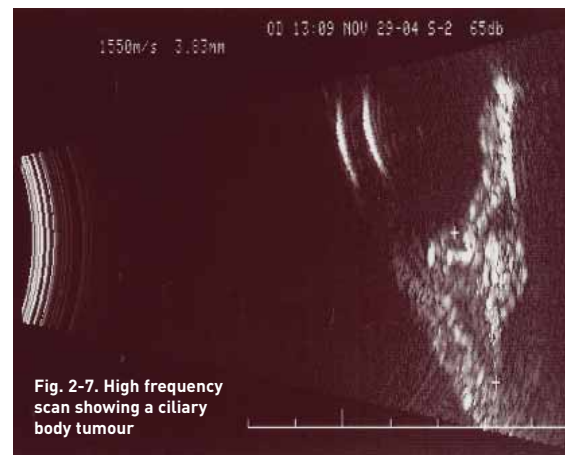
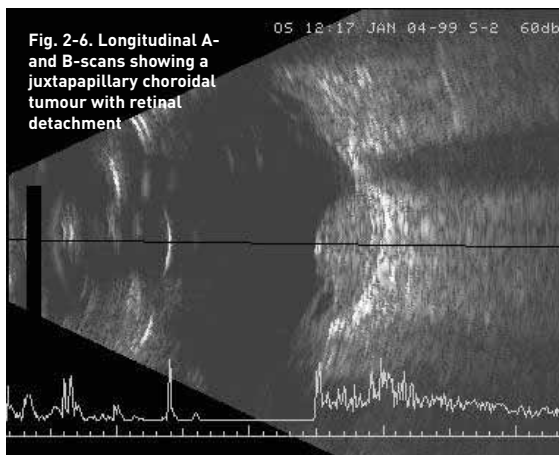
The scan positions can be longitudinal, transverse, oblique, and axial. The desired scan is obtained by tilting, sliding and twisting the probe.

To scan a tumour located far from the macula, we ask the patient to look in the direction of the tumour, for example, to the left if the lesion is located temporally in the left eye or nasally in the right eye.

When searching for a tumour, for example, one thought to be located nasally, the patient is asked to look nasally with that eye. We start by performing a transverse scan of the macula, with the probe touching the limbus, then we slide the probe slowly back to the equator of the eye while tilting the probe to screen that quadrant of the eye as far anteriorly as ciliary body. If the media are opaque, this procedure is repeated performing a longitudinal scan and in all the principal directions of gaze.

**When assessing a tumour, we:**

- Reduce the gain as much as possible, to improve resolution
- Measure the tumour thickness, ensuring that the probe is at right angles to the tumour, that the thickest point is measured, and that the callipers are correctly positioned at the internal scleral surface and tumour apex, taking account of any retinal detachment
- Measure the largest basal tumour diameter as well as the longitudinal and transverse basal dimensions. Care is taken not to over-estimate tumour size in the presence of retinal detachment and not to under-estimate basal diameter if the tumour margins are tapering
- Measure the distance between tumour and centre of disc. Do this by keeping the disc in view while twisting the probe until the tumour appears.
- Assess internal tumour spread
- Look for extraocular tumour spread, taking care to differentiate tumour from oblique muscle
- Assess internal acoustic reflectivity noting: whether sound attenuation is marked or gradual; whether the reflectivity is low, medium or high (compared to retroocular fat) and regular or irregular. Look for spontaneous movement, such as shimmering caused by blood flow
- Look for echo mobility by asking the patient to look from side to side as the scan is taken
- Assess the vitreous, increasing the gain



When comparing sequential measurements, it is essential to consider measurement variation and to look for a trend over several weeks or months before deciding whether or not the tumour is growing or regressing.

### COMPUTERISED TOMOGRAPHY (CT)

The indications for computerized tomography are limited as far as uveal tumours are concerned, because ultrasonography is usually adequate. For example, although computerised tomography nicely demonstrates bone in a choroidal osteoma, similar information can be obtained less expensively and more conveniently with ultrasonography.

### MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging with fat suppression and contrast agent can be useful in selected cases.

Melanin has peculiar paramagnetic features, being hyperintense and hypointense with respect to vitreous in T1 and T2 images respectively; however, as mentioned above, not all melanocytic tumours are melanoma and not all melanomas are pigmented.

With conjunctival tumours, MRI scans may be indicated if the tumour is believed to involve the orbit, either primarily or secondarily.

## BIOPSY

### Extraocular Tumours

- Incisional biopsy. This is indicated for diffuse conjunctival disease, such as primary acquired melanosis, both at initial presentation and after treatment. Multiple biopsies are needed to assess the extent and severity of disease. We believe that it is unsafe to perform incisional biopsy of nodular tumours, such as melanoma, because this procedure may encourage seeding of tumour cells to other parts of the conjunctiva and nasolacrimal duct. Care is taken not to cause crush artefact, when holding the specimen and placing it on a paper mount
- Excisional biopsy. This is my preferred technique for any nodular lesions. A no-touch technique is used if possible. The instruments are replaced with a fresh set for tissue closure, to prevent tumour seeding. Care is taken not to cause crush artefact
- Imprint cytology. This is no longer used at our centre, because it does not provide information about the depth of tumour spread

Immunohistochemistry helps to distinguish malignant cells from normal tissues when assessing conjunctival biopsies.

Several patients have had multiple conjunctival melanomas after undergoing incisional biopsy or excision at their local hospital before referral to our centre. My suspicion is that this problem is iatrogenic.

### Intraocular Tumours

#### Briefly, the various techniques include:

- Fine needle aspiration biopsy (FNAB), performed with a 25-gauge needle, which is passed either through pars plana opposite to the tumour or through the sclera at the base of the tumour. The main limitation is an insufficient tumour sample. Vitreous haemorrhage is common but usually mild, resolving spontaneously in a few days. Retinal detachment is rare, even though a retinal hole is created over the tumour. Except for retinoblastoma, the risk of tumour seeding is small
- 20-G vitrector biopsy has been described, the procedure including total vitrectomy and measures to prevent retinal detachment. (Bechrakis, Foerster, & Bornfeld 2002)

- 25-G vitrector biopsy is our preferred technique, which we have used exclusively since September 2004. It is performed using three trans-conjunctival scleral cannulae (for endoillumination, infusion and the vitreous cutter). Vitrectomy, tamponade and retinopexy are not required. It is occasionally necessary to suture a scleral opening if leakage is apparent. This procedure is relatively quick and simple. The main problem is vitreous haemorrhage, especially if the tumour is small so that normal choroidal blood vessels are damaged
- Incisional biopsy, through a scleral flap, is no longer performed by the author because it is more difficult and time consuming than the 25-G system
- Excisional biopsy is performed when there is diagnostic uncertainty and when local resection is the treatment of choice in any case

**Our indications for tumour biopsy include:**

- Uncertain diagnosis despite full clinical examination
- Confirmation of the suspected diagnosis if requested by the patient
- Characterisation of type of metastasis, in the absence of any detectable extraocular primary tumour
- Molecular typing of uveal melanoma, for example, detecting chromosomal abnormalities related to metastatic spread. We perform these studies only if there is surplus tissue when biopsy is undertaken for diagnostic reasons; this may change if studies in progress indicate that all patients would benefit

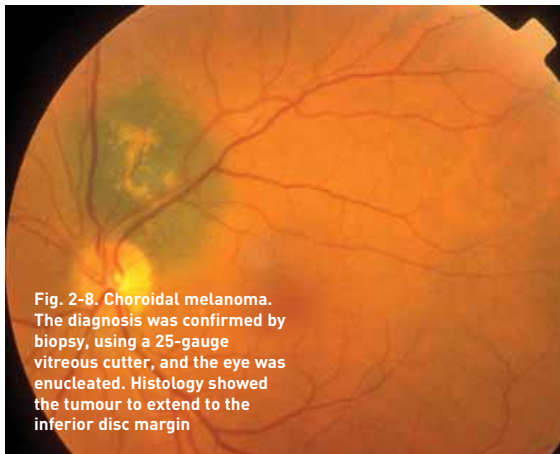


Fig. 2-8. Choroidal melanoma. The diagnosis was confirmed by biopsy, using a 25-gauge vitreous cutter, and the eye was enucleated. Histology showed the tumour to extend to the inferior disc margin

## FOLLOW-UP

All patients are routinely asked about their general health, visual symptoms, ocular discomfort and concerns about possible ocular complications and survival. This is done with the help of a proforma in the casenotes, which ensures that all questions are asked in a systematic fashion and that all answers are documented properly.

This process often reveals problems that might not come to light if patients are merely asked how they are. For example, it is not uncommon to discover that a patient is worrying unduly about metastatic disease despite having previously been advised of an excellent prognosis for survival.

## SYSTEMIC EXAMINATION

Routine examination is performed for anaesthetic reasons. Any additional assessment relating to a specific ocular diagnosis or differential diagnosis is described in the section dealing with that tumour.

## DOCUMENTATION

All information is documented in the casenotes using proformas we have designed for our ocular oncology service. Drawings are used as much as possible.

This information is also computerised into our ocular oncology database, usually by the consultant in the ocular oncology clinic. All such entries are subsequently checked for accuracy and completeness by a full-time data manager.

# PATIENT REFERRAL

## REFERRAL BY OPTOMETRIST

We suggest that optometrists refer patients with suspected malignancy directly to an ophthalmologist, informing the general practitioner of the referral. Unless local guidelines dictate otherwise, the patient could be advised to attend an ophthalmic casualty and given a letter to take to the hospital. Our impression is based on our audit, which indicates that many patients experience significantly longer delays when referred to hospital via their general practitioner rather than directly. (Damato 2001a; Damato 2001b)

Symptomatic benign tumours should be referred urgently via the general practitioner, if it is possible to be confident about the diagnosis.

Asymptomatic benign tumours should be referred non-urgently via the general practitioner. Again, the optometrist must be certain that the tumour is benign if there is any possibility that the patient may need to wait several weeks or months before being seen by an ophthalmologist.

## REFERRAL BY CASUALTY AND PRIMARY CARE UNITS

Specialist Registrars and Senior House Officers seeing a patient with suspected malignancy in a casualty or primary care clinic should try to arrange for the patient to see a consultant the same day, or if this is not possible within a week.

## REFERRAL BY CONSULTANT OPHTHALMOLOGIST

**Patients should be referred to an adult ocular oncology centre if they have:**

- Suspected ocular malignancy, such as: (a) uveal melanoma; (b) adenocarcinoma; (c) lymphoma; and (d) metastasis (unless the patient is already being treated for systemic metastases and no specialist advice is required)
- Melanocytic choroidal tumours with thickness exceeding 2 mm, collar-stud shape, documented growth, clumps of orange pigment, serous retinal detachment, or visual symptoms
- Melanocytic iris tumours that are more than 3 mm in diameter, markedly elevated, involving the angle or associated with secondary glaucoma
- Suspected conjunctival malignancy, such as: (a) melanoma; (b) squamous cell carcinoma; (c) primary acquired melanosis with atypia; (d) ocular surface squamous neoplasm; (e) conjunctival sebaceous carcinoma; and (f) other rare conjunctival tumours
- Conjunctival melanocytic tumour if: involving cornea, palpebral conjunctiva or caruncle; associated with feeder vessels; nodule is associated with diffuse pigmentation; or diameter exceeds 3 mm in the absence of clear cysts
- Any ocular tumour that cannot be diagnosed with certainty, such as: (a) indeterminate pigmented lesions; (b) eccentric disciform lesions; and (c) combined hamartoma of the retina and retinal pigment epithelium



Fig.-3-1. Ocular Oncology Office, with Clerk, Specialist Nurse, Data Manager, Personal Assistant, Consultant, Ophthalmic Sister, Compliance Officer and Oncology Photographer. The Health Psychologist has her own office to ensure privacy for patients. The Ophthalmic Sister's desk is shared with the Oncology Fellow

- Benign ocular tumours that require skills or equipment not usually available in a general ophthalmic clinic, such as: (a) choroidal haemangioma; (b) retinal haemangioblastoma; (c) vasoproliferative tumour; and (d) conjunctival papilloma

**Patients should not be referred to an adult ocular oncology centre if they have the following conditions:**

- Typical naevus
- Primary acquired melanosis without atypia (if biopsy has been performed)
- Eyelid and orbital tumours

**When the patient is sent to a specialist ocular oncology service, the referral letter should include:**

- An explicit statement of patient referral
- The patient's demographic details, particularly the home, work and mobile phone numbers
- The main clinical findings
- The results of any investigations performed
- What the patient has been told
- Any special needs or preferences that the patient might have
- The NHS number, if this is readily available
- The general practitioner's name and address and if possible the fax number
- The referring consultant's name and address and fax number (sometimes the referral letter contains only the name of an SHO or SpR, who may no longer be working with the same consultant once the patient is discharged from the oncology centre)

If possible, this letter should be dictated onto its own tape and typed within a day. Ideally, the letter should be faxed and a copy should be sent by mail. The NHS Cancer Plan specifies that referrals for possible cancer should reach the specialist hospital within 24 hours of the decision to refer.

If the patient is being referred after tumour growth has been confirmed by sequential examination, a copy of any baseline colour photograph would be helpful.

It would be prudent for the referring ophthalmologist's secretary to phone the oncology service to ask about waiting times or any other aspects of care that are considered important. The patient should be given a number to phone if an appointment letter is not received within two weeks. It is the responsibility of the referring hospital or general practitioner to organise transport for patients needing this service.

### HANDLING OF REFERRAL BY ONCOLOGY CENTRE

Within one or two days of receipt of the referral letter, fax or telephone call the oncology secretary will give the patient an appointment date. If possible, this will be done by telephone to determine the patient's availability without delay and to identify any special needs and preferences.

The secretary will mail a letter to the patient confirming the time and place of the appointment, together with any information leaflets, guides and questionnaires prepared for this purpose.

**The ocular oncology service in Liverpool does not accept referrals from:**

- Optometrists, who are encouraged to refer patients to their local ophthalmologist
- General practitioners, unless the patient has already been seen by an ophthalmologist and if a second opinion is requested
- SHOs, SpR's and other non-consultants, unless the patient has been seen by a consultant

The patient's referral should not be delayed because ocular investigations or results are awaited.



# MANAGEMENT

## UVEAL MELANOMA

### Introduction

Several therapeutic modalities in the management of uveal melanoma have evolved over the past few decades. Previously, there was much debate as to which was best; however, there is a general trend towards a multimodality approach, selecting between different forms of treatment according to the size and shape of the tumour, taking the patient's own priorities into account (e.g. vision vs local tumour control). Furthermore, different forms of treatment are now being combined to achieve higher rates of local tumour control while minimising complications.

### Influencing Survival

Attitudes regarding the scope of treating primary uveal melanomas have changed dramatically and there is still no consensus on this matter.

For many years, it was believed that urgent and radical treatment of uveal melanoma was life-saving. Then, in 1978, Zimmerman and colleagues hypothesised that enucleation actually caused early metastatic death, either by disseminating tumour cells or by interfering with immunological or other defence mechanisms. (Zimmerman, McLean, & Foster 1978)

This belief encouraged the development of measures such as pre-enucleation radiotherapy. This has, however, since been found to be ineffectual. (Hawkins 2004) Several studies have now shown that the survival probability after conservative forms of therapy is no worse than after enucleation. (Diener-West et al. 2001)

It is well known that even taking lead-time bias into account, large tumour size correlates statistically with death from metastatic disease. There are currently two schools of thought regarding the significance of this finding.

According to the prevailing hypothesis, uveal melanomas become more life-threatening as they grow larger, because they de-differentiate and have a larger volume.

Proponents of this view therefore tend to treat large tumours more aggressively and urgently than small

melanomas, some of which are even left untreated for months of years until growth is documented. (The Collaborative Ocular Melanoma Study Group 1997)

An alternative hypothesis, which is the one I support, is that there are two types of uveal melanoma: (a) low-grade, 'good' melanomas, which are slow-growing, with little or no metastatic potential; and (b) high-grade, 'bad' melanomas, which grow rapidly and which metastasize early.

According to this school of thought, differentiation into good or bad melanoma occurs early. This implies that it is the small, high-grade melanomas that should be treated most urgently and aggressively, because it is with these tumours that any opportunities for preventing metastatic spread are greatest. With large, high-grade tumours, systemic metastases are probably already present so that ocular treatment is perhaps only palliative.

A problem with the latter approach (i.e. treating small tumours aggressively) is that relatively few small melanomas are likely to be high-grade, because those that are aggressive have probably grown by the time of diagnosis. This means that unless the grade of melanoma can be determined before treatment, for example, by cytogenetic studies on a tumour sample, most patients with a small tumour will be over-treated, with many suffering unnecessary ocular morbidity and visual loss.

Knowledge regarding the molecular biology and progression of uveal melanomas is still too limited to influence treatment planning. For example, if biopsy is undertaken in a patient with a small melanoma and if the result suggests that this tumour is 'low-grade', the chances of a sampling error occurring are not known. Furthermore, it is uncertain as to whether a low-grade melanoma can ever transform into a high-grade, lethal variety if left untreated.

Until it is established whether metastatic spread commences before or after a uveal melanoma attains a large size, it would seem prudent to treat all patients urgently and aggressively. If treatment is delayed, for example, to document definite growth, then the patient

must be informed that the risk of withholding treatment is not known and this should be recorded in the casenotes. Similar precautions are necessary if in order to conserve vision the patient is given a treatment that carries an increased risk of local tumour recurrence.

Now that studies have established that survival after conservative treatment of uveal melanoma is not significantly worse than after enucleation, the debate has moved on.

An ongoing controversy relates to whether local treatment failure ever causes metastatic disease or whether any recurrence is merely an indicator of increased tumour malignancy at the time of initial treatment. Until this question is answered, practitioners and patients are obliged to base their therapeutic decisions on what amounts to intuitive impressions regarding the impact of ocular treatment on survival.

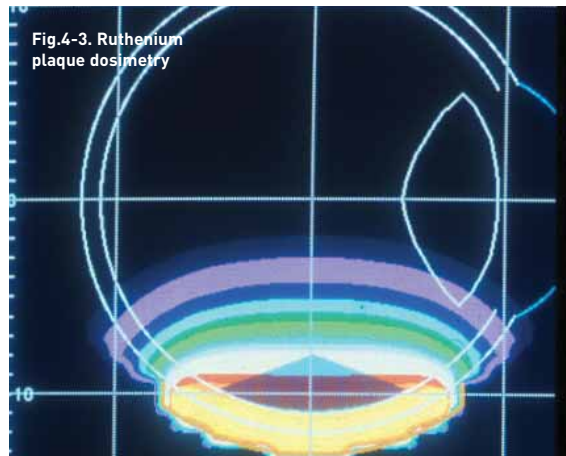
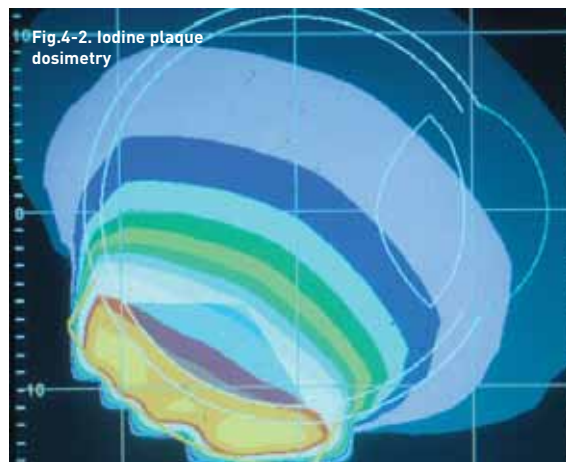
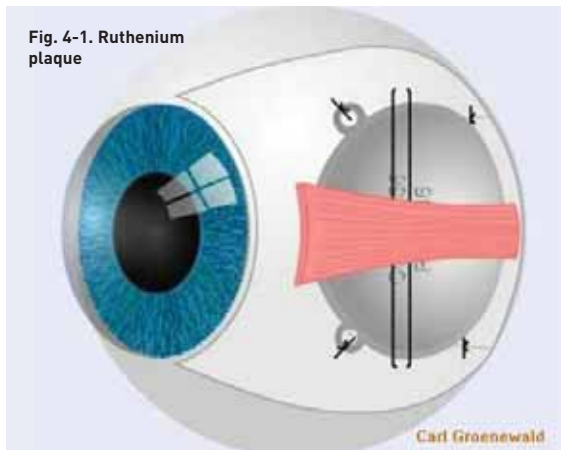
**Brachytherapy**

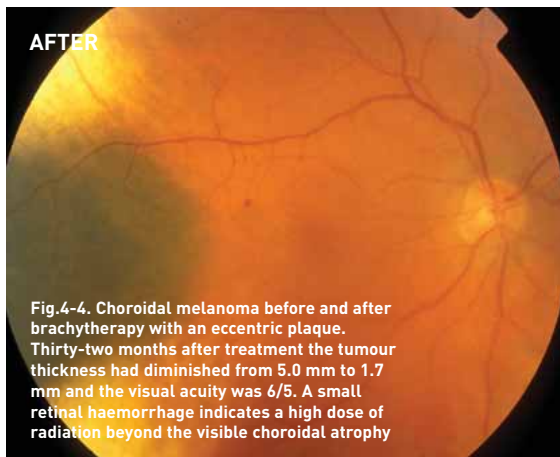
In most centres, the first choice of treatment is brachytherapy, which is administered with a radioactive plaque containing ruthenium-106 or iodine-125. A few centres use combined ruthenium and iodine plaques, or isotopes such as palladium or strontium.

Iodine plaques emit gamma irradiation and can successfully treat tumours as thick as 10 mm; however, they deliver large doses of radiation to

healthy ocular structures. A collimated plaque has recently been designed to reduce side-scatter of radiation to healthy ocular tissues. Iodine plaques are available in Liverpool but are avoided if possible because of the extensive radiation retinopathy we have seen after their application.

Ruthenium plaques are suitable for uveal melanomas up to 6 mm in thickness, because of the limited range of beta radiation they emit. It is not possible to collimate the radiation to reduce collateral damage to optic disc and fovea; however, we have developed a technique for positioning the plaque eccentrically, with its posterior edge aligned with the posterior tumour margin.





The results of eccentric plaque placement in terms of local tumour control and conservation of vision compare favourably with other studies.(Damato et al. 2005c;Damato et al. 2005d) For example, the actuarial eight-year rate of local tumour control was about 100 percent except in patients whose tumour diameter exceeded 11 mm, in which case it was around 90 percent. However, there is scope for randomised, prospective studies.

Brachytherapy is often administered in combination with transpupillary thermotherapy, either to prevent local tumour recurrence or as a treatment for exudative maculopathy.

In Liverpool, brachytherapy is the first choice of treatment for choroidal tumours up to 6 mm in thickness, unless there is extension close to the optic disc, in which case proton beam radiotherapy might be preferred. As mentioned above, the plaque is positioned eccentrically if the tumour extends far posteriorly. Checks are performed intraoperatively to confirm that the plaque is positioned correctly, using a right-angled transilluminator and a perforated template we developed.

#### Proton Beam Radiotherapy

Proton beam radiotherapy enables a high dose of radiation to be aimed precisely at a uveal melanoma irrespective of the tumour's size, shape and location.

Facilities for this treatment are available in only a small number of centres around the world. Some oncologists use proton beam radiotherapy for all choroidal melanomas; we in Liverpool reserve it for tumours that cannot adequately be treated by brachytherapy, that is, tumours that are large or those that extend close to the optic disc or fovea.(Damato et al. 2005a) Our audits indicate that our 10-year actuarial rate of local tumour control is approximately 98 percent.

In 1994, we started treating iris melanomas with proton beam radiotherapy, thereby avoiding the problems of iridectomy and iridocyclectomy.(Damato et al. 2005b) Our publication reported that in 88 patients with iris melanoma, only three eyes were lost and this was because of advanced or diffuse disease. The main

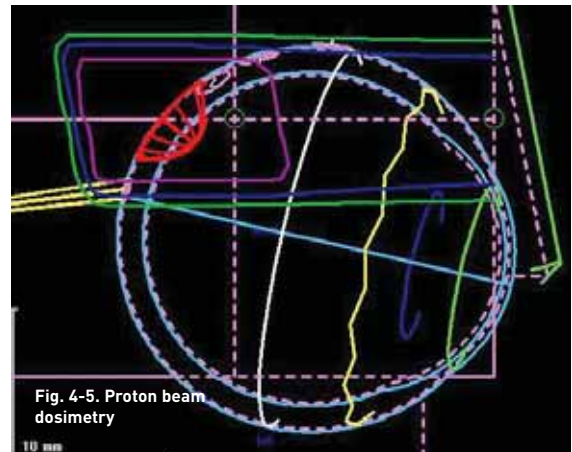




Fig. 4-6. Iris melanoma with secondary glaucoma, before and after proton beam radiotherapy. More than five years after treatment the eye was comfortable with vision of 6/6+, the intraocular pressure having been controlled by trabeculectomy and medical treatment. We expect that cataract will develop one day

problems were cataract, which was eminently treatable, and glaucoma, which was in several patients present at the time of initial presentation. Although a comparative study was not performed, my clinical impression is that the results of proton beam radiotherapy are superior to my results with iridectomy and iridocyclectomy.

For several years, we have in selected cases combined proton beam radiotherapy with transpupillary thermotherapy, either to reduce the lateral safety margin if the tumour extends close to optic nerve or as a treatment for exudative maculopathy. Our results so far have been most encouraging and I hope these can be evaluated and published in a formal manner before long.

Proton beam radiotherapy of large uveal melanomas is often complicated by persistent exudative retinal detachment, rubeosis and neovascular glaucoma. In Liverpool, we have found that these complications can be treated successfully by removing the irradiated tumour by trans-scleral local resection or endoresection. (Damato & Foulds 2006)

#### **Stereotactic Radiotherapy**

With stereotactic radiotherapy, a highly collimated beam of photons or gamma radiation is aimed at the tumour from many different directions so that a high dose of radiation is delivered to the melanoma while exposing healthy tissues to small doses of radiation. (Dieckmann et al. 2003) This approach is generally used as an alternative to proton beam radiotherapy, in centres where a cyclotron unit is not available. This treatment is not used in Liverpool.

#### **Photocoagulation**

Photocoagulation of uveal melanoma is associated with a high complication rate and has been superseded by transpupillary thermotherapy.

#### **Transpupillary Thermotherapy (TTT)**

With transpupillary thermotherapy, the tumour is heated by only a few degrees for about one minute by means of a 3 mm diode laser beam, administered using a contact lens. (Journee-de Korver, Midena, & Singh 2005) The power of the laser is adjusted so that retinal blanching does not develop for at least 40 seconds. The effects of transpupillary thermotherapy extend to a depth of up to 4 mm. Adjunctive brachytherapy is advocated as a means of avoiding local tumour recurrence from intra-scleral tumour ('sandwich technique'). (Bartlema et al. 2003)

In Liverpool, TTT is used as a secondary treatment after radiotherapy (1) if there is uncertainty about adequacy of radiotherapy, or (2) as a treatment for exudation, either at the time of presentation or when exudation develops after treatment.

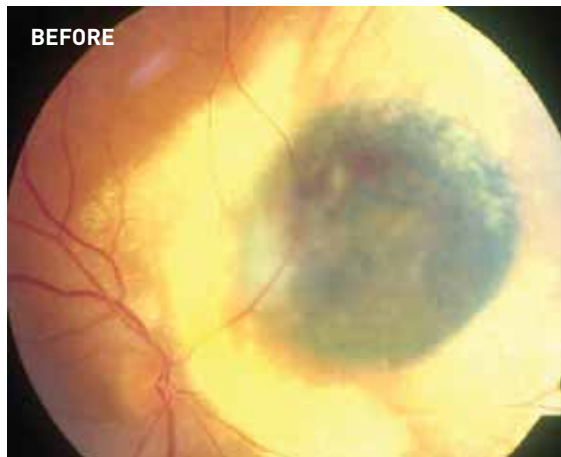


Fig. 4-7. Exudation from an irradiated choroidal melanoma, with resolution after transpupillary thermotherapy of the 'toxic' tumour

Transpupillary thermotherapy alone is associated with a high rate of local tumour recurrence. (Shields et al. 2002) We therefore no longer administer TTT as a primary treatment for choroidal melanoma unless (1) the patient has a limited life expectancy, (2) the patient is diabetic (so that there is an increased risk of radiation retinopathy), has a small tumour and accepts that TTT is not as reliable as radiotherapy, and (3) the patient has an indeterminate melanocytic choroidal tumour but does not accept monitoring after being informed of uncertainty regarding the hazards of such management.

### Photodynamic Therapy (PDT)

Photodynamic therapy using Verteporfin has recently been described but it is still too soon to assess the efficacy of this treatment, both as primary therapy for melanoma and as adjunctive treatment for exudation. We have treated one patient with PDT after proton beam radiotherapy, with apparent benefit.

### Cryotherapy

Cryotherapy can be effective for choroidal melanomas. (Wilson & Klein 2002) However, this form of therapy has not gained widespread acceptance.

### Trans-Scleral Local Resection

Trans-scleral local resection of small, ciliary body melanomas has been performed for many years. Advances in microsurgery and hypotensive anaesthesia have also made it possible to remove large tumours extending as far posteriorly as the fovea. This operation is difficult and therefore performed only in a few centres, such as Liverpool, where it is reserved for tumours that are considered too large for radiotherapy. (Damato & Foulds 2006)

The main complications are local tumour recurrence and rhegmatogenous retinal detachment. Tumour control has improved with adjunctive brachytherapy and by restricting this surgery to tumours less than 17 mm in diameter. Surgical refinements have reduced the incidence of retinal tears and in the event of a retinal break immediate vitreoretinal surgery at the end of the local resection is highly successful at preventing retinal detachment.

Our audit results indicate that we are able to conserve about 90 percent of eyes that would otherwise be enucleated, with local tumour control rates of less than 10 percent and conservation of central or peripheral vision depending on the proximity of the tumour to the fovea.

An advantage of local resection is that it provides tumour tissue for cytogenetic studies thereby refining prognostication.

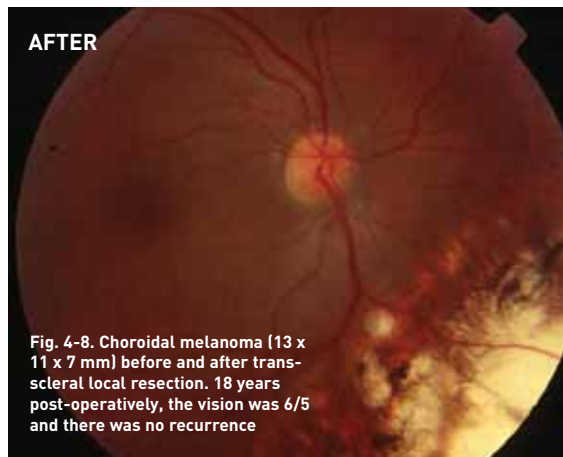
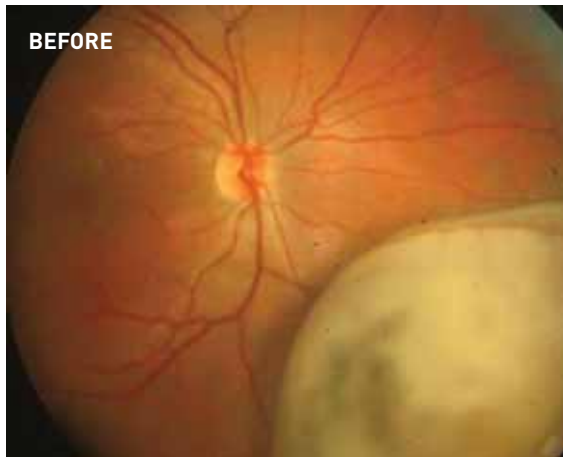


Fig. 4-8. Choroidal melanoma (13 x 11 x 7 mm) before and after trans-scleral local resection. 18 years post-operatively, the vision was 6/5 and there was no recurrence

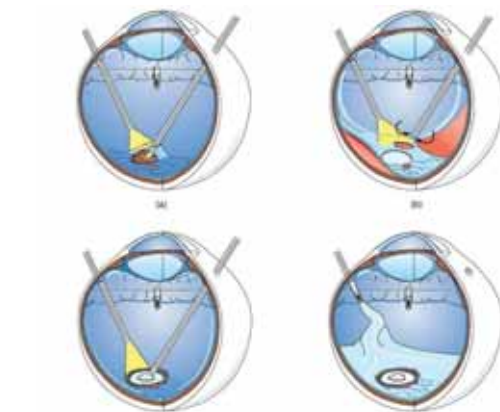


Fig. 4-9. Endoresection of choroidal melanoma

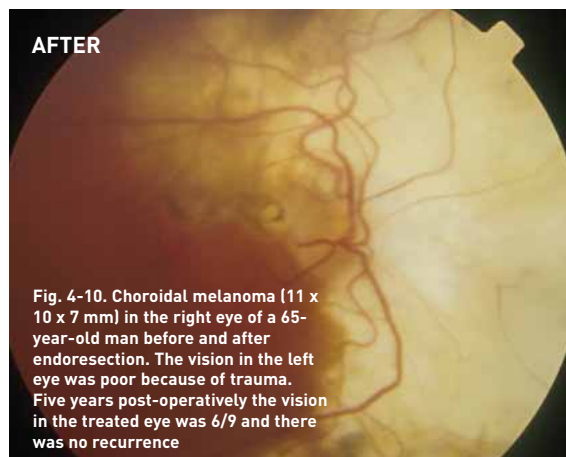


Fig. 4-10. Choroidal melanoma (11 x 10 x 7 mm) in the right eye of a 65-year-old man before and after endoresection. The vision in the left eye was poor because of trauma. Five years post-operatively the vision in the treated eye was 6/9 and there was no recurrence

### Endoresection

With endoresection, the uveal melanoma is removed with a vitreous cutter, either through a hole in the retina or after raising a retinal flap. (Damato et al. 1998)

Primary endoresection is controversial because of concerns about tumour seeding. Our own audit results indicate that rates of local tumour control achieved by endoresection compare well with other methods. However, until this operation is more widely accepted, I feel we should perform this operation only with juxtapapillary tumours when other methods are unlikely to conserve vision.

Endoresection is also effective as a treatment for exudation after radiotherapy.

We administer adjunctive radiotherapy after the endoresection whenever possible. Others give proton beam or stereotactic radiotherapy before the endoresection. (Bornfeld et al. 2002) The main complication has been retinal detachment but this problem has been overcome by performing indentation at the time of gas fill and treating any tears with cryotherapy.

### Enucleation

Primary enucleation for uveal melanoma is now performed only when other methods are considered unlikely to conserve the eye and useful vision without causing excessive morbidity; and/or if the patient is not motivated to try to save the eye or feels comfortable with this choice. The author currently performs primary enucleation in about 34 percent of all patients with uveal melanoma, mostly because patients present at a late stage. (Damato & Lecuona 2004)

The enucleation is performed in the standard fashion, using the surgeon's preferred implant. To ensure that the correct eye is removed, the tumour is visualised by binocular indirect ophthalmoscopy, which is done after draping the patient and covering the other eye.

### In Liverpool, enucleation is performed with:

- Disposable instruments because of the risk of transmitting prion infections
- Retrobulbar anaesthetic with adrenaline to prevent intraoperative haemorrhage, the oculo-cardiac reflex and post-operative pain
- A hydroxyapatite implant, or perhaps an acrylic implant if the patient consents to participation in a randomised, prospective study currently in progress

### Ocular Results of Conservative Therapy

The ocular results of conservative therapy are usually reported in terms of local tumour control, visual acuity, ocular conservation and complications such as exudative or rhegmatogenous retinal detachment, neovascular glaucoma, cataract and phthisis.

### Clinical features predicting ocular outcomes include:

- Largest basal tumour diameter
- Tumour thickness
- Distances to optic disc and fovea
- Retinal invasion
- Extra-ocular spread
- Exudative retinal detachment

Systemic factors such as diabetes influence the outcome after radiotherapy. The degree of tumour malignancy, as indicated by cell type and cytogenetics, is important but not usually known at the time of primary treatment.

### Management of Systemic Metastasis

There is debate about the scope of screening for metastatic disease at the time of initial treatment of the ocular tumour and subsequently. Some screen all patients indiscriminately whereas others target only high-risk patients.

The method of screening is also controversial. Biochemical liver function tests performed annually are of little value. To detect pre-symptomatic metastases, it is necessary to perform six-monthly LFT's combined with some form of liver imaging. (Eskelin et al. 1999) There is growing interest in investigations such as PET (positron emission tomography) scans, which can reveal occult extrahepatic metastases, thereby sparing the patient futile liver surgery.

Regular screening is undertaken in the hope that metastatic disease would be more treatable if detected early. However, even with intensive investigation, few patients are treatable by partial hepatectomy. Treatment with other methods is generally disappointing. (Singh & Borden 2005)

In Liverpool, patients have cytogenetic testing if treated by local resection or enucleation or if a 25-G tumour biopsy is performed. Those with disomy 3 melanoma are reassured and those with a monosomy 3 tumour are referred to an oncologist at Clatterbridge Centre for Oncology for advice about screening for metastatic disease (with referral to a local oncologist if they live too far away to attend Clatterbridge).

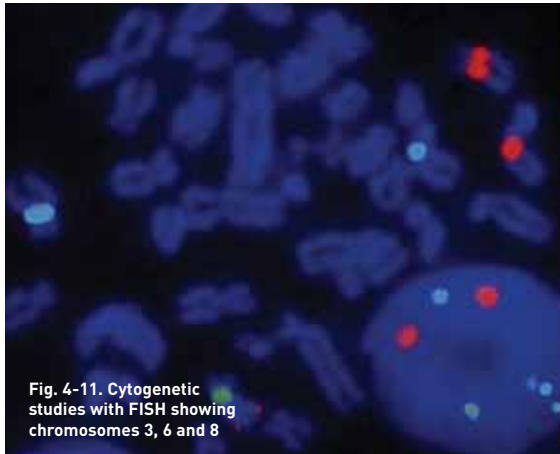


Fig. 4-11. Cytogenetic studies with FISH showing chromosomes 3, 6 and 8



Fig. 4-13. Information kiosk in the outpatient waiting area

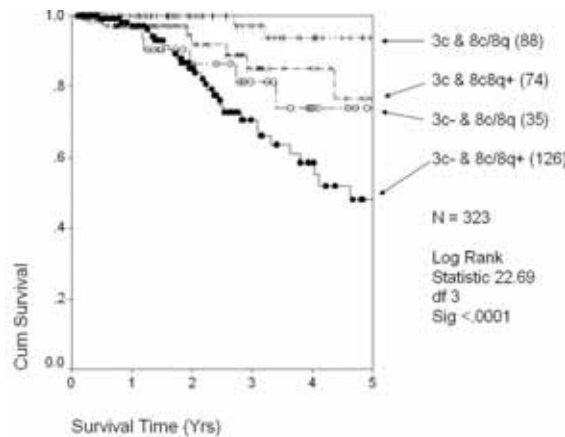


Fig. 4-12. Metastatic death according to cytogenetic results. This audit includes only patients from mainland Britain, because with this group the NHS Cancer Registry automatically notifies us of the date and cause of any deaths

**Counselling**

Paternalistic treatment has been superseded by greater patient involvement in decision-making. This demands better communication and can be more stressful for patients, but ultimately results in greater patient satisfaction.

In Liverpool, all new patients are given an audio-cassette tape recording of their initial explanation, to help them remember what was said at their first consultation and we provide a player if necessary. A kiosk has been installed in the outpatient waiting area for patients and their relatives to view an interactive program, which includes animated graphics of the various forms of treatment.

All patients (i.e. new referrals and those being followed up) receive copies of all clinic and discharge letters to the GP and referring ophthalmologist (but not pathology and cytogenetic reports, because any upsetting results are best given in person).

There is growing awareness of the psychological morbidity that patients and their relatives experience and these issues are being addressed more fully. In Liverpool, all patients are screened by a health psychologist for psychological morbidity and appropriate care is organised if indicated, if necessary in liaison with the general practitioner.

The specialist ocular oncology nurse also plays an important role, for example: (a) speaking to each patient immediately after the initial consultation; (b) visiting all patients in the ward; (c) telephoning every patient a few days after discharge from hospital; (d) providing a telephone help-line; and, on request, (e) arranging for new patients to speak to similar patients who have previously had the same treatment.

**Future Developments**

All too many patients present to an oncology service only when their tumour has reached an advanced stage, by which time opportunities for conserving the eye and vision are diminished. There is scope for enhancing awareness of the clinical features that can alert the practitioner to the presence of an ocular tumour.

There is a need for adjuvant systemic therapy in high-risk patients, starting this treatment as early as possible. Possible therapies include systemic chemotherapy, immunotherapy, anti-angiogenic agents and perhaps controversially Cox-2 inhibitors. Large, multicentre, randomised, prospective studies are required to evaluate the efficacy and safety of such agents.

### CHOROIDAL NAEVUS

Choroidal naevi are reported to occur in about 10 to 20 percent of the population, with about 90 percent developing posterior to the equator.

We classify pigmented choroidal tumours into two categories: (a) typical naevi, which are small, flat and

grey; and (b) atypical naevi, which are dome shaped and pigmented or amelanotic. Atypical lesions are either: (i) non-suspicious; or (ii) suspicious of malignancy. Suspicious features are: (a) thickness greater than 2 mm; (b) serous retinal detachment; (c) confluent orange pigment; (d) symptoms, such as photopsia; and (e) contact with optic disc. (Shields et al. 1995b)

#### Diagnosis

Symptoms such as blurred vision, metamorphopsia and photopsia (i.e. a 'ball of light') are noted. Binocular indirect ophthalmoscopy is performed, documenting the clinical features with photography.

#### Management

##### Typical naevus

Patients are informed of any typical naevi, with reassurance that these are extremely common and insignificant. The presence of any naevi is documented in the casenotes.

##### Atypical naevus

The diameter of the lesion is documented with colour photography and, if possible, the thickness is measured with ultrasonography, obtaining measurements from the internal scleral surface.

Surveillance of the lesion is organised, which should be life-long, with review every four to six months, then once a year for a year or two, and then every two years. Comparison of the ophthalmoscopic appearances with a baseline colour photograph greatly enhances the



Fig. 4-14. Typical choroidal naevus

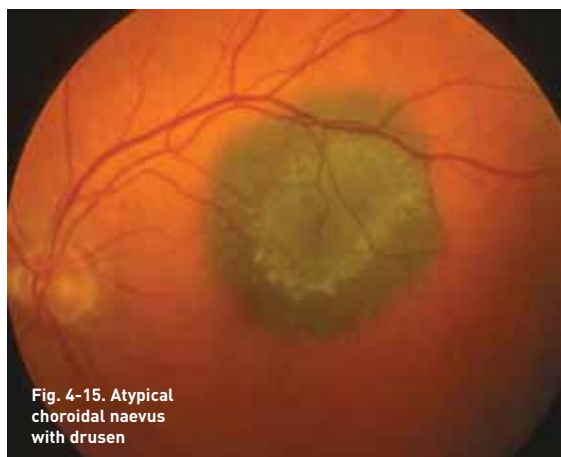


Fig. 4-15. Atypical choroidal naevus with drusen

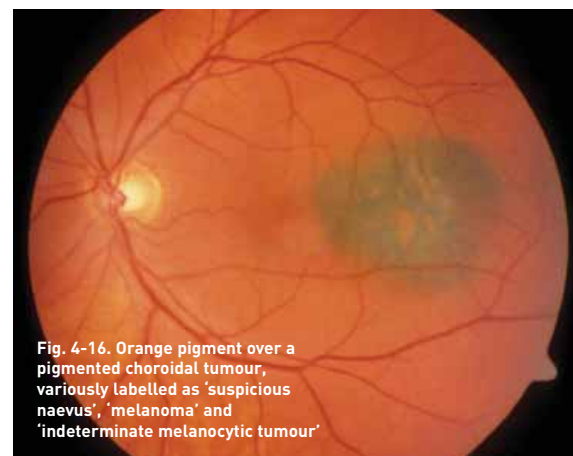


Fig. 4-16. Orange pigment over a pigmented choroidal tumour, variously labelled as 'suspicious naevus', 'melanoma' and 'indeterminate melanocytic tumour'

ability to detect subtle change. It is preferable but not essential to repeat the photography and ultrasonography at each visit.

This monitoring could be undertaken by the referring ophthalmologist or by an optometrist close to the patient's home, in which case the patient should be referred formally to a named optometrist by means of a letter.

The optometrist should acknowledge receipt of the letter, in writing. The optometrist should be provided with a baseline colour photograph, either automatically or upon request.

If tumour growth occurs or if suspicious features develop, the tumour is considered as malignant and treated as such.

#### **Choroidal naevus with features suspicious of malignancy**

If a melanocytic tumour shows any features of malignancy, the patient is informed that the tumour may or may not be malignant and the reasons are given. The chances of malignancy increase with the number of suspicious features present.

The choice of management is between: (a) immediate treatment, accepting that such therapy and any resulting morbidity and visual loss may prove to be unnecessary; and (b) surveillance, proceeding to treatment only once growth is documented.

The selected management will be decided on the basis of: (a) the number of suspicious features and hence the likelihood of malignancy; (b) the size and location of the tumour and therefore the chances of visual loss if treatment were to be administered; (c) the visual needs, determined by occupation and status of the fellow eye; (d) the life-expectancy; and (e) the patient's attitude to risk.

To be able to provide informed consent for treatment or non-treatment, the patient needs to understand that: (a) only a minority of small melanomas (i.e. less than 10 mm in diameter and less than 3 mm thick) ever develop the capacity to metastasize, many only causing ocular damage; (b) it is not known when

metastatic spread begins to occur, although some have suggested that tumour dissemination starts when the tumour diameter is very small; and (c) the treatment of metastatic disease is essentially palliative.

The patient is given the choice of attending an ocular oncology service for counselling and possible treatment, which may consist of transpupillary thermotherapy, plaque radiotherapy, or proton beam radiotherapy.

It is not conventional practice to obtain signed informed consent for non-treatment of a possible malignancy. Nevertheless, it is important to document what was said to the patient, both in the case sheets and in the clinic report to the general practitioner, preferably sending a copy of such a report to the patient. If a copy of the letter is mailed to the patient, this should be recorded on all copies of this letter by appending the patient's name and address in the usual manner.

#### **MELANOCYTOMA**

Melanocytomas are usually seen at the optic disc but can arise anywhere in the uveal tract.

This kind of tumour can show malignant growth, either because of malignant transformation or if a melanoma has mistakenly been diagnosed as melanocytoma. Melanocytomas can grow slowly, may extend extraocularly and can also undergo necrosis to cause



Fig. 4-17. Melanocytoma, with no change after several years

pigment dispersion, as well as: (a) optic nerve compression and acute visual loss if the tumour is located at the optic disc; and (b) uveitis and glaucoma if it is situated in ciliary body. Patients with such a tumour are managed in the same way as those with a suspicious naevus.

### MELANOCYTOSIS

Ocular melanocytosis and oculo-dermal melanocytosis (i.e. Naevus of Ota) are associated with an increased risk of uveal melanoma. There is an association between melanocytosis and bilateral Sturge-Weber syndrome.

#### Diagnosis

**Diagnosis is based on any of the following:**

- Iris heterochromia
- Slate-grey episcleral pigmentation
- Skin pigmentation around eye
- Choroidal pigmentation

This condition should not be confused with conjunctival melanosis.

#### Management

Ocular melanocytosis is managed in the same fashion as a naevus with features suspicious of malignancy. Multiple ocular melanomas can occur in this condition.

### CHOROIDAL HAEMANGIOMA

Choroidal haemangiomas are rare, benign tumours, which usually develop posteriorly, near the optic disc or fovea. They can be focal or diffuse, the latter occurring in association with the Sturge-Weber Syndrome.

A choroidal haemangioma can remain asymptomatic or can cause exudative retinal detachment, with visual loss and eventually painful neovascular glaucoma.

#### Diagnosis

Full ophthalmic examination is performed. Ultrasonography can be useful if performed and interpreted with sufficient expertise. Fluorescein angiography is not helpful. Although indocyanine green angiography provides characteristic appearances, this investigation is rarely necessary.

#### Management

##### Focal

If a focal haemangioma is asymptomatic, treatment is not necessary so that the patient can either be: (a) discharged, with appropriate advice on what to do if symptoms develop; or (b) reviewed after six months and then once every year or two.

In any case, precautions are made to avoid delays in treatment should symptoms develop, because the chances of therapy improving vision diminish if visual loss is severe and/or prolonged.



Fig. 4-18. Ocular melanocytosis involving the episclera and part of the iris

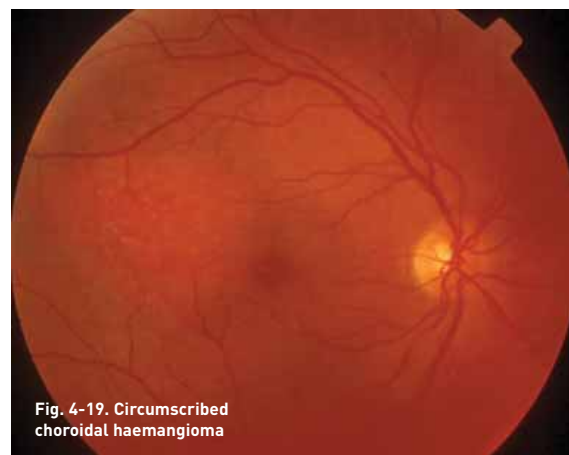


Fig. 4-19. Circumscribed choroidal haemangioma

For small choroidal haemangiomas, up to 10 mm in diameter, the first choice of therapy is now photodynamic therapy, because it avoids the visual loss caused by transpupillary thermotherapy and the inconvenience and expense of brachytherapy, photon therapy, or proton beam radiotherapy.(Madreperla 2001)

It may be necessary to repeat the photodynamic therapy once or twice, if symptoms and tumour bulk persist after more than two months.

#### Diffuse

Diffuse choroidal haemangiomas are usually extensive and often associated with a bullous retinal detachment so that the chances of phototherapy being successful are diminished. Plaque radiotherapy is usually not possible because of optic disc involvement.

The choice of treatment, therefore, is between photon therapy and proton beam radiotherapy. The latter is more expensive and may be more inconvenient for the patient, but it greatly reduces radiation exposure to extraocular tissues and hence any risk of malignancy developing after several decades. This risk, however small, needs to be communicated to the patient and of course the parents in the case of children.

Some patients might prefer not to have any treatment at all if there is no rubeosis iridis and if the likelihood of improving vision is considered to be small. Such procrastination is reasonable and acceptable, although it would be advisable to monitor the patient, with reviews every six months initially and eventually once a year.

Once improvement has been documented after completion of any treatment, the patient can be discharged, with full advice on what to do if any symptoms develop. Patients are warned before leaving the centre that visual loss can occur after several years, because of subretinal fibrosis or retinal pigment epithelial atrophy.

## CHOROIDAL OSTEOMA

Choroidal osteoma can affect the fovea both directly and by inducing choroidal neovascularisation.(Aylward et al. 1998) Spontaneous regression of choroidal osteoma can occur in a minority of cases.

#### Diagnosis

Ultrasonography is useful, showing the high acoustic reflectivity of the tumour surface, with orbital shadowing.

Multiple small choroidal lesions similar to osteomas can arise in sclero-choroidal calcification.

#### Management

Regression of choroidal osteoma has been reported after photocoagulation and after corticosteroid therapy.



Fig. 4-20. Choroidal osteoma

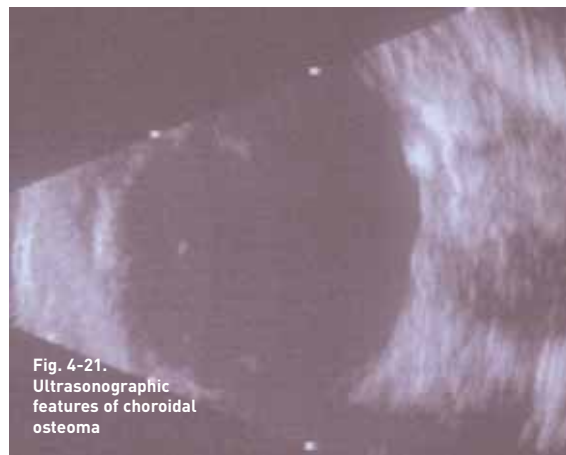


Fig. 4-21. Ultrasonographic features of choroidal osteoma

These treatments can be attempted if the tumour is impinging on the fovea to cause symptoms. Any choroidal neovascularisation causing visual loss is treated in the usual way. The patient should be advised of a guarded visual prognosis.

### NEUROFIBROMA, NEURILEMMOMA AND LEIOMYOMA

#### Diagnosis

These tumours usually develop in ciliary body. Although clinical features allow a tentative diagnosis, histology is required for confirmation. Most are diagnosed after local resection or excision biopsy.

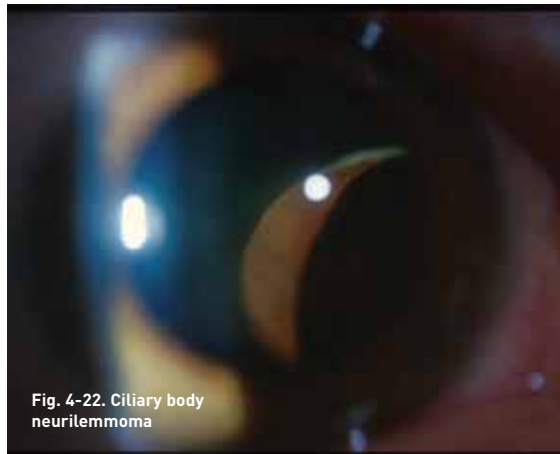


Fig. 4-22. Ciliary body neurilemmoma



Fig. 4-23. Astrocytic hamartoma

#### Treatment

Treatment is by trans-scleral local resection, which is a specialised procedure.

### ASTROCYTIC HAMARTOMA

This benign retinal hamartoma usually occurs in children in association with tuberous sclerosis, but a solitary lesion can arise at any age in otherwise healthy individuals.

#### Diagnosis

Systemic disease is excluded by: (a) dermatological examination; (b) MRI brain scan for intra-cranial lesions; (c) family studies; and (d) molecular genetic studies. These are organised in collaboration with a geneticist.

#### Treatment

Most astrocytic hamartomas are static and asymptomatic. Any vitreous haemorrhage, neovascular glaucoma and optic nerve damage may be treated empirically, albeit with a guarded prognosis.

### RETINAL HAEMANGIOBLASTOMA

#### Diagnosis

After detecting any retinal angiomas, three-mirror examination is performed to detect early lesions, which may resemble microaneurysms. Fluorescein angiography has also been recommended for this purpose.



Fig. 4-24. Retinal haemangioblastoma

Retinal haemangioblastoma can develop in isolation or in association with von Hippel Lindau syndrome. The patient therefore requires: (a) a family history; (b) a full medical and neurological examination; (c) MRI scans of the CNS and abdomen; (d) measurement of the blood pressure; (e) 24-hour urinary vanillyl mandelic acid (VMA); and (f) detection of VHL mutations by means of genetic studies. The patient can be referred to a clinical geneticist for all these assessments to be performed.

### Management

#### Ocular disease

Patients require ophthalmoscopy every six months between the age of 10 and 30 years and annually at all other ages. At each ophthalmic review, the patient should: (a) give a history, with specific questions looking for intracranial disease (headache, dizziness, nausea, vomiting), spinal disease (pain, weakness and loss of sensation in arms and legs), pheochromocytoma (palpitations and sweating attacks), endolymphatic sac tumour (deafness and loss of balance), pancreatic disease (gastrointestinal symptoms) and renal cell carcinoma (red urine/haematuria); (b) have blood pressure measurement for pheochromocytoma; (c) urinalysis for renal carcinoma; and (d) ophthalmoscopy for retinal angioma and disc swelling (for intracranial disease).

Retinal lesions can be treated with: (a) photocoagulation or cryotherapy if small, depending on whether they are posterior or anterior, respectively; or (b) ruthenium plaque radiotherapy if more than 1-2 DD in size; or (c) with vitreoretinal surgery if vitreous bands and tractional retinal detachment are present.

Suggested treatments for juxtapapillary lesions include: VEGFR-1 inhibitors; argon and diode laser photocoagulation; and photodynamic therapy. The prognosis is poor using conventional methods.

#### Systemic disease

Patients with von Hippel-Lindau disease require: (a) annual physical examination; (b) annual urinary and blood catecholamine levels; (c) two-yearly brain MRI; (d) two-yearly abdominal ultrasonography; and (e) ear MRI and audiometry if deafness is present. These investigations are undertaken by the geneticist. Family studies are also needed.

## RETINAL CAVERNOUS ANGIOMA

### Diagnosis

#### The diagnosis is based on:

- Ophthalmoscopic appearances
- A positive family history
- Epilepsy and other disease caused by intracranial lesions
- Capillary angiomas on neck or trunk

The patient and close relatives require neurological examination with MRI scans.

#### Treatment of Ocular Lesions

Photocoagulation of retinal lesions, is avoided because it can result in haemorrhage and tumour enlargement.

## RACEMOSE ANGIOMA

### Diagnosis

**The ocular features are characteristic. We look for proptosis and optic atrophy. Intracranial disease is excluded by performing:**

- Neurological examination
- Perimetry
- MRI brain scan

#### Treatment

No ocular treatment is required unless there are complications, which are treated as appropriate.

Patients are advised about the risk of haemorrhage after dental extraction, which can occur if there are any vascular malformations in the jaw.

### VASO-PROLIFERATIVE TUMOUR

This is a pink/yellow tumour usually located inferiorly, temporally and anteriorly. (Shields et al. 1995a) This condition may arise in isolation or in association with other ocular conditions, such as uveitis, previous retinal detachment, ocular trauma and retinitis pigmentosa. The main problem is the formation of hard exudates, which cause maculopathy and visual loss. Advanced tumours can cause total retinal detachment and neovascular glaucoma.

Treatment is by (a) cryotherapy or (b) ruthenium plaque radiotherapy. There may be scope for surgical removal of exudates if these threaten the macula. The visual prognosis is poor.

There is scope for investigating the use of anti-angiogenic agents, intravitreal steroids, removal of epiretinal membranes and any hard exudates threatening the fovea. There is also scope for assessing the value of surgical removal of the tumour in advanced cases.

### RETINOBLASTOMA

This disease only rarely affect adults. It can do so in the following manner: (a) development of a secondary malignant neoplasm of the orbital region or ocular adnexa after previous radiotherapy; (b) detection of an inactive tumour, consisting either of a benign variant of retinoblastoma or a spontaneously regressed tumour, with both of these varieties threatening tumour

recurrence; (c) development of adult retinoblastoma, which is usually peripheral and often associated with clinical features resembling uveitis; and (d) development of retinal vasculopathy or cataract after previous treatment of retinoblastoma. Adult patients with retinoblastoma are usually referred from Liverpool to a centre specialising in the treatment of this disease.

### CHRPE

Solitary and clustered lesions (i.e. 'bear tracks' or 'cat's paws') do not have any systemic associations, but the presence of more than three atypical, spindle-shaped lesions affecting one and both eyes is associated with familial adenomatous polyposis (FAP), which predisposes to colon carcinoma.

### Diagnosis

Three-mirror examination is performed, first, to confirm that the lesion is flat and, second, to detect atypical lesions associated with FAP, if there is any reason to suspect this condition.

Nodular tumours arising from CHRPE have recently been described and these are believed to be adenomas or adenocarcinomas. For this reason, there is scope for organising life-long surveillance, possibly with ophthalmoscopic examination every one or two years. The patient could be referred to an optometrist for this monitoring, if the optometrist can provide evidence that he or she can undertake this duty.



Fig. 4-25.  
Asymptomatic  
retinoblastoma in a 17-  
year-old woman



Fig. 4-26. CHRPE

## CYSTS

### Diagnosis

Slit-lamp examination is performed with 3-mirror examination after mydriasis to determine whether the cyst arises in (a) pupil margin, (b) iris pigment epithelium, (c) ciliary epithelium, (d) iris stroma, or (e) conjunctiva (i.e. implantation cyst). Exclude associated conditions such as: (a) life-threatening, dissecting aortic aneurysm in the case of autosomal familial iris flocculi; (b) associated tumours such as naevus, melanoma and medulloepithelioma; (c) secondary glaucoma and cataract.

### Treatment

Asymptomatic cysts can be observed.

Symptomatic epithelial cysts can be ruptured with argon or Nd-YAG laser treatment.

Stromal iris cysts can be destroyed by collapsing the cyst by needle aspiration and performing cryotherapy or injecting alcohol, which is removed after a few minutes. This treatment may need to be repeated. Implantation cysts can be locally resected.

## ADENOMA AND ADENOCARCINOMA

These two tumours arise from retinal pigment epithelium, ciliary epithelium, CHRPE or from chorioretinal scars and form part of a continuous spectrum. They can be pigmented or amelanotic and are difficult to differentiate clinically from melanoma.

### Diagnosis

These tumours tend to be diagnosed histologically, after resection.

### Treatment

Although observation has been recommended, most tumours are treated by iridocyclectomy, which is useful both for diagnostic and therapeutic purposes.

## COMBINED HAMARTOMA OF THE RPE AND RETINA

This rare condition can affect the juxtapapillary retina or can be peripheral.

### Diagnosis

The diagnosis is based on ophthalmoscopy.

### Treatment

Recurrent vitreous haemorrhage from a peripheral lesion can be prevented by cryotherapy.

Occasionally, epiretinal membrane surgery can improve vision. Occlusive therapy of the fellow eye has been recommended for children with visual loss.



Fig. 4-27. Iridociliary cyst



Fig. 4-28. Combined hamartoma

## MEDULLOEPITHELIOMA

This is derived from retina and ciliary epithelium and usually presents in childhood. Very rarely, it can become manifest in adulthood.

### Diagnosis

The diagnosis is based on slit-lamp examination and high-frequency ultrasonography. Possible secondary effects, such as glaucoma, cataract and retinal detachment, need to be excluded.

### Treatment

Observation has been suggested for small, non-growing tumours. Localised lesions can be resected, but there is a high risk of local recurrence.

Diffuse, large or recurrent tumours are treated by enucleation, with exenteration if there is orbital extension, because of the risk of intracranial spread, which can be fatal.

## INTRAOCULAR METASTASIS

### Introduction

Intraocular metastases are common but usually overshadowed by the systemic disease. Most uveal metastases arise in breast and lung, less common sites being gastrointestinal tract, kidneys and prostate. Metastases tend to grow relatively fast and to cause an extensive exudative retinal detachment. Most metastases respond to radiotherapy.

### Diagnosis

Ultrasonography is performed mostly to determine the size and extent of the tumour. Although internal acoustic reflectivity can be of diagnostic value, this assessment requires experience and is regarded as a specialist examination.

If the patient does not have any previous history of malignancy, a comprehensive assessment is performed including: (a) full systemic history; (b) general medical examination, including rectal examination and breast or scrotal palpation; and (c) chest radiography.

Further investigations, such as: mammography; brain MRI; bone scan, sputum cytology; CT scans of chest, abdomen and pelvis; faecal occult blood; serum carcinoembryonic antigen (CEA); prostatic serum antigen (PSA) and CA125 for ovarian cancer are considered. Urgent advice of an oncologist is obtained, either by referring the patient or by telephone.

If the patient does have a history of previous malignancy, the patient is referred urgently back to his or her usual oncologist for further management. Postal delays are avoided by making the referral by fax or phone. The patient should be seen by the oncologist within two weeks of receipt of referral.

If tumour biopsy may be required to establish the diagnosis of malignancy or to indicate the type of cancer, this is performed with a 25-gauge vitrector.



Fig. 4-29. Metastasis from breast



Fig. 4-30. Metastasis from lung

Before performing the biopsy, we liaise with the pathologist to determine what should be done with the sample and to decide whether or not the pathologist is to be present at the operating theatre to confirm that an adequate specimen has been obtained.

It is up to the ophthalmologist responsible for the patient's care to decide whether he or she should perform the biopsy or whether the patient should be referred to an ocular oncologist or vitreoretinal surgeon.

The main objectives of referring a patient to an ocular oncologist are: (1) to confirm or refute a suspected diagnosis; and (2) to recommend treatment, also deciding with the patient where such therapy should be delivered. The referral is made by fax or phone to avoid postal delays, because ocular metastases can grow rapidly.

### Management

The management of ocular metastases is palliative so that total tumour eradication is not of vital importance. The choice of management depends on the size and location of the metastasis, the presence or absence of symptoms and the life-expectancy.

If the metastasis is small and asymptomatic, then local treatment is not necessary, especially if the patient is undergoing systemic therapy.

Most patients receive external beam radiotherapy, which is delivered either over four weeks, if the life-expectancy is good, as with breast carcinoma, or over five days if the prognosis for survival is poor. If the patient lives far from the ocular oncology centre, this external beam radiotherapy is best delivered at a hospital near the patient's home.

If the tumour is small and further than 2 disc diameters from the optic disc then the ocular oncologist may attempt photodynamic therapy or transpupillary thermotherapy (depending respectively on whether or not the tumour extends close to fovea) in the hope of sparing the patient from the inconvenience of external beam radiotherapy.

If the tumour is small and far from optic disc and fovea, plaque radiotherapy may be performed, either as a primary procedure or if other methods have failed.

The patient is reviewed about six weeks after treatment to ensure that there has been an adequate response. For all treatments other than external beam radiotherapy there is a significant risk of local relapse, with rapid growth of any recurrent tumour. Therefore, the patient is either reviewed regularly or advised how to obtain an urgent ophthalmic appointment should any symptoms develop (e.g. attending their local eye casualty).

As a rule, all follow-up is at the local hospital, especially if the patient is unwell. Feedback to the ocular oncologist is desirable, for audit purposes.

## PRIMARY CNS/INTRAOCULAR LYMPHOMA

### Ocular Assessment

Primary intra-ocular lymphoma usually involves the retina but may rarely arise in uvea. Retinal lymphoma is considered in any patient with vitreous cells and multifocal, white or yellow, subretinal tumours. (Jahnke et al. 2005) We examine for complications such as macular oedema, exudative retinal detachment, retinal arteriolar occlusion and optic neuropathy, which results in optic atrophy.

It is essential to confirm the diagnosis by biopsy, reducing the chances of a false negative result by: (a) stopping steroid treatment several days before; (b) obtaining an adequate sample of vitreous and of any bulky subretinal deposits, using a 25-gauge vitrector; (c) liaising with the pathologist to ensure that the specimen is treated properly (e.g. using an appropriate fixation solution) and is received by the pathologist as soon as possible after collection. The patient is referred to an oncologist for confirmation of the diagnosis.

### Systemic Assessment

A full medical examination is undertaken. Neurological assessment is also performed, looking for signs of an intracranial mass, leptomeningeal disease, and spinal cord disease. If the diagnosis of primary intraocular lymphoma is confirmed, the patient requires regular: (a) neurological examination; (b) contrast-enhanced MRI brain scan; (c) lumbar puncture; (d) chest x-ray; (e) abdominal CT scan; and (f) bone marrow biopsy. The patient is referred to a haematologist or oncologist with a special interest in lymphoma for management.

### Ocular Treatment

Treatment of the primary intraocular lymphoma can be either: (a) external beam radiotherapy (40–50 Gy); or (b) a course of intravitreal methotrexate injections (particularly for solitary ocular recurrence). It would be more convenient for the patient if any such treatment were to be administered at the local hospital. There is a recent trend towards systemic therapy, which not only improves the ocular status but also delays the development of CNS lymphoma.

### Systemic Treatment

Most patients with primary intraocular lymphoma develop CNS disease within a short time. This has a high mortality, despite treatment consisting of: (a) radiotherapy to brain and spinal cord; and/or (b) high dose systemic and intrathecal chemotherapy. There is no consensus as to whether treatment should be given prophylactically or only when clinical disease develops.

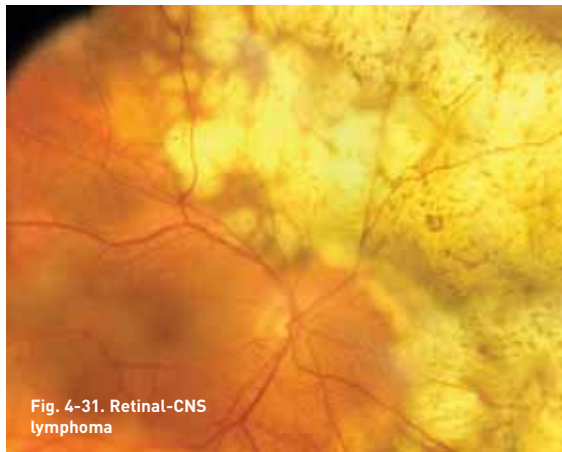


Fig. 4-31. Retinal-CNS lymphoma

## OTHER HAEMATOLOGICAL MALIGNANCIES

### These include:

- Secondary intraocular lymphoma
- The leukaemias
- Cutaneous T cell lymphoma
- Multiple myeloma
- And, exceptionally rarely, Hodgkin's lymphoma

### Examination

#### We look for:

Tumour deposits, such as:

- Choroidal tumours in secondary lymphoma
- Retinal flecks
- Perivascular infiltrates
- Vitreous cells
- Pseudohypopyon
- Optic nerve infiltration

Circulatory abnormalities, such as:

- Retinal haemorrhages
- Cotton wool spots
- Roth spots
- Microaneurysms caused by hyperviscosity in multiple myeloma

Exudation, with:

- Optic disc oedema
- Exudative retinal detachment
- Pars plana cysts in multiple myeloma

Opportunistic infections, such as cytomegalovirus, toxoplasmosis, aspergillus and cryptococcus.

Extraocular abnormalities should be noted, such as: (a) proptosis; (b) herpes zoster ophthalmicus; (c) perilimbal infiltrates; and (d) graft-vs-host disease after allogeneic bone marrow transplantation.

## PARANEOPLASTIC SYNDROMES

These syndromes are rare but may allow early detection and treatment of the underlying neoplasm. They include: (a) cancer-associated retinopathy, which affects primarily the retina; (b) bilateral diffuse uveal melanocytic proliferation (BDUMP), involving mostly the choroid; and (c) miscellaneous other abnormalities, such as optic neuropathy.

### Assessment

Noted symptoms of visual loss, night blindness, photopsia, and any previous history of malignancy, particularly cutaneous melanoma. Look for: (a) RPE stippling, red/grey patches, depigmented areas; (b) attenuation and perhaps sheathing of retinal vessels; (c) optic atrophy; (d) multiple pigmented and amelanotic tumours; (e) vitreous cells; (f) exudative retinal detachment; (g) cataract; and (h) glaucoma.

Organise: (a) colour photography; (b) fluorescein angiography; (c) ultrasonography, including high-frequency examination of ciliary body; and (d) electrophysiology.

A full medical examination is performed, noting any vitiligo. Refer the patient to an oncologist for further investigation. An occult primary neoplasm can sometimes be detected only after repeated examinations.

### Treatment

Successful treatment of the primary tumour can result in regression of the ocular manifestations. Systemic steroids, plasmapheresis, and intravenous immunoglobulins can be tried but the results are unpredictable.

## CONJUNCTIVAL MELANOMA

Conjunctival melanoma is rare.(Brownstein 2004) Although local excision may seem straightforward, special precautions are needed to prevent seeding.

### Examination

As already mentioned in this text, we feel that incisional biopsy may complicate subsequent management.

### Management

Nodular melanomas are excised, if possible with a wide safety margin of about 2 mm and without fragmenting the lesion. If the tumour is adherent to the underlying sclera, this is excised by performing lamellar scleral dissection. Some advocate cryotherapy to the scleral base and surrounding conjunctiva. Using

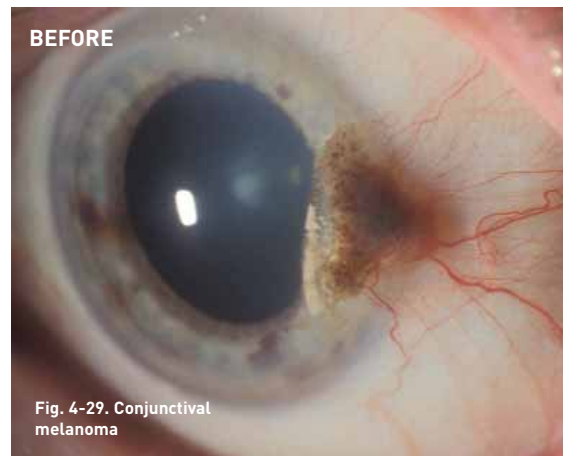
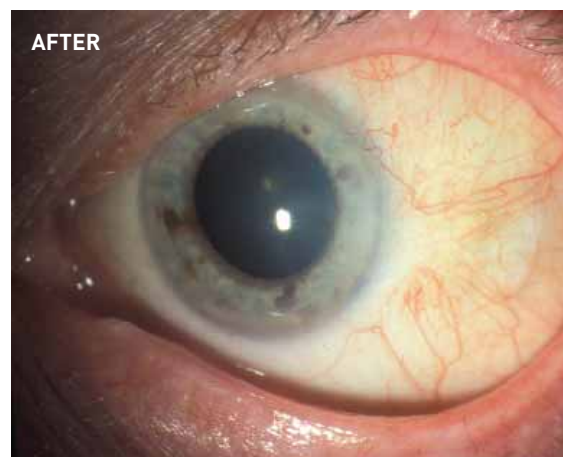


Fig. 4-29. Conjunctival melanoma



separate instruments, the conjunctival defect is reduced as much as possible, if necessary leaving part of the wound to heal by second intention so as not to deform the fornices. In Liverpool, we have not needed to use an amniotic graft. The tumour with a rim of normal tissue is placed onto a card and into fixative, taking care not to cause crush artefact.

Once the conjunctiva has healed, brachytherapy is administered if histological examination shows deep invasion. The patient is given a course of mitomycin C drops if there is diffuse superficial disease. Proton beam or other radiotherapy may be useful for forniceal disease.

The patient is reviewed every six months for one or two years and then annually. Areas of confluent or increasing pigmentation are biopsied in case further treatment is necessary because of recurrent disease. At each visit, the regional nodes are palpated and the patient is asked about general health.

If enlarged regional nodes develop, the patient is referred to a head and neck surgeon for excision biopsy and radiotherapy.

If there is any suspicion of systemic disease, the patient is referred to an oncologist.

## CONJUNCTIVAL NAEVUS

### Assessment

Full conjunctival examination is performed, documenting the lesion with a conjunctival drawing, if possible also taking colour photographs. There are no data to indicate whether the patients with an unequivocal naevus need surveillance by an ophthalmologist or whether they can safely be entrusted with self-monitoring and discharged.

### Treatment

There is no consensus as to whether or not naevi should be excised prophylactically, specifically for the purpose of preventing melanoma. Many patients wish to have a conjunctival naevus removed for cosmetic reasons.



Fig. 4-33. Naevus of plica, with cysts

## PRIMARY ACQUIRED CONJUNCTIVAL MELANOSIS

### Assessment

A history is taken to ensure that the melanosis is acquired. The extent of the lesion is documented with a conjunctival drawing, and if possible, with colour photography. Multiple conjunctival micro-biopsies are necessary to determine whether or not there is atypia. The biopsies are taken under local anaesthesia and are about 3 mm in diameter to provide an adequate specimen without the need for suturing.

Each specimen is grasped at one point only, placed on a card without vigorous spreading so as to avoid crush artefact, and immersed in formalin in a separate container, with careful labelling. Immunohistochemistry is required to identify and localise atypical melanocytes, differentiating these from normal epithelial cells and identifying early stromal invasion. Assessment of the degree of malignancy requires the input of an experienced pathologist.

### Treatment

If there is melanosis without atypia, no treatment is required. It is uncertain as to whether ophthalmic surveillance and repeat biopsies are required and, if so, at what intervals. Intuitively, patients could be reviewed once a year with biopsies being taken only if the melanosis has increased.



If there is melanosis with atypia, then treatment is required. Local excision with adjunctive cryotherapy has been recommended for small areas of PAM with atypia. In most patients, the disease is too extensive for excision and topical chemotherapy with mitomycin C is preferable.

After treatment, patients are reviewed every six months for a year or two, then once every year for about five years and eventually once every two years. Biopsies are indicated only if the melanosis increases.



### SQUAMOUS PAPILLOMA

The tumour is diagnosed from its slit-lamp appearance and categorised as pedunculated or sessile and as single or multiple.

Various treatments have been described, which include: (a) excision with cryotherapy; (b) interferon alpha; (c) oral cimetidine; (d) mitomycin C drops; and (e) laser photocoagulation.

### OCULAR SURFACE SQUAMOUS NEOPLASIA

This can be regarded as a carcinoma in situ, confined to the epithelium. (Pe'er 2005) It can progress to invasive squamous cell carcinoma.

#### Assessment

To differentiate this condition from a Pagetoid variety of sebaceous carcinoma, it is necessary to perform multiple biopsies, using immunohistochemistry.

#### Management

Because of the diffuse nature of this lesion, complete excision is difficult so that recurrences are common without adjunctive cryotherapy. An alternative approach is to rely on topical chemotherapy with mitomycin C or 5-fluorouracil. Brachytherapy can also be useful for recurrent lesions.

Surveillance is required after treatment and should be life-long.

### INVASIVE CONJUNCTIVAL CARCINOMA

#### Assessment

It is noted whether the tumour is focal, diffuse or mixed. (Pe'er 2005) Anterior segment examination is performed to exclude intraocular spread, which causes glaucoma and pseudo-uveitis. The regional nodes are palpated.

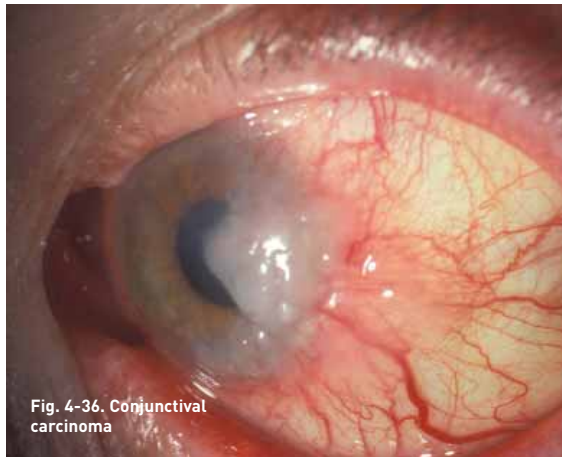


Fig. 4-36. Conjunctival carcinoma



Fig. 4-37. Conjunctival lymphoid tumour

#### Management

The standard treatment is local excision of any nodules. Some advocate histological assessment of clearance with frozen sections at the time of surgery. If the cornea is involved, Bowman's layer is conserved as this is a barrier to intraocular spread. Adjunctive cryotherapy, radiotherapy or topical chemotherapy with 5-FU may reduce the chances of recurrence. Advanced disease may require enucleation or exenteration.

After treatment, life-long surveillance is required as recurrence can occur after many years.

#### BENIGN CONJUNCTIVAL LYMPHOID TUMOUR

This is also known as 'reactive lymphoid hyperplasia' of the conjunctiva. It is indistinguishable clinically from malignant lymphoma. (Coupland, Hummel, & Stein 2002)

#### Assessment

The extent of the disease is documented with drawings and if possible colour photographs. An incisional biopsy is performed to determine whether the tumour is benign or malignant.

#### Management

Treatment is given only if the disease is uncomfortable or if there is a threat of malignancy. Topical antibiotics have been found useful and are tried in an attempt to avoid radiotherapy.

#### CONJUNCTIVAL LYMPHOMA

##### Assessment

The extent of the disease is defined, carefully examining the fellow eye and palpating the regional nodes.

The patient requires biopsy to confirm malignancy and to subtype the tumour in the case of malignant lymphoma. The vast majority of conjunctival lymphomas are of B-cell type, and the three most common are the following: (a) extranodal marginal zone B-cell lymphoma (i.e. MALT lymphoma); (b) follicle centre lymphoma; (c) diffuse large cell lymphoma. An important differential diagnosis is mantle cell lymphoma, which is an aggressive subtype of small cell B-cell lymphomas.

Pathological investigations might include: (a) demonstration of monoclonality by immunohistochemistry and with the polymerase chain reaction technique; (b) characterisation of type of lymphocytic proliferation (i.e. B cell vs T cell); (c) assessment of tumour cell proliferation rate; (d) tumour cell expression of p53; as well as (e) the presence of CD5+ tumour cells. It is advisable to consult the pathologist before doing the biopsy to ensure that the sample is handled correctly.

If the diagnosis of lymphoma is confirmed, the patient will require staging assessments and perhaps systemic treatment. (Coupland, Hummel, & Stein 2002) The patient is referred to a haematologist or oncologist with a special interest in this disease.

#### **Treatment**

Low grade lymphomas can be observed without therapy or treated with external beam radiotherapy. Topical antibiotics may be tried.

High grade lymphomas require external beam radiotherapy, which may be combined with systemic chemotherapy. Life-long follow-up is required.

#### **ONCOCYTOMA**

This rare tumour is usually benign but can very rarely be malignant, especially if arising away from the caruncle. Treatment is by local resection.

#### **SEBACEOUS GLAND CARCINOMA**

In the absence of a nodular eyelid tumour, Pagetoid spread of sebaceous gland carcinoma across the conjunctiva can occur de novo. (Shields et al. 2005) This condition is considered in any patient with unilateral blepharoconjunctivitis, especially if this does not resolve with standard treatment.

Biopsy is necessary to confirm the diagnosis, using special lipid stains and immunohistochemistry. The regional nodes are palpated for metastases.

Surgical excision is not usually possible because the disease is extensive. Recently, success has been reported with topical chemotherapy, which may avoid the need for exenteration. Life-long monitoring is needed. The five-year mortality is about 15 percent.

#### **KAPOSI SARCOMA**

This tumour is suspected in immunocompromised individuals presenting with apparent subconjunctival haemorrhage, pyogenic granuloma or foreign body granuloma. It would be useful to confirm the diagnosis by incisional or excisional biopsy.

The tumour may regress if the patient receives anti-viral treatment, perhaps for newly diagnosed AIDS. Otherwise, low-dose external beam radiotherapy (8 Gy in a single fraction) is usually successful. Other methods described include interferon, cryotherapy and surgical excision.

#### **CHORISTOMA**

Troublesome limbal choristomas can be excised by lamellar dissection, being prepared to perform corneal or scleral grafting. Excision of supero-temporal dermolipoma is avoided as this can be followed by ptosis, dry eye and limitation of eye movements.

# THE CARE PATHWAY

This chapter summarises the care of patients with uveal melanoma, this being the commonest condition treated. The care pathway of patients with other conditions is similar.

## THE REFERRAL PROCESS

### The ocular oncology secretary:

- Telephones the patient to arrange an appointment and to identify any specific needs.
- Mails a package, which includes information sheets, demographics questionnaire, guidebook, and research consent form.
- Organizes accommodation at a nearby hotel or at Royal Chambers, an apartment block across the street from the hospital. These facilities are part of the Royal Liverpool University Hospital.

## INITIAL ASSESSMENT

The initial assessment clinic is held every Monday morning, when 10 to 20 new patients are usually seen. If there are too many referrals in any one week or if the Lead Clinician is about to be absent from the Unit, then new patients are also seen in the follow-up clinic, which is held on Thursday.

On arrival, the patient is received by the oncology clerk, who works full time in the oncology service and who has prepared the casenotes. The clerk checks all the details and retrieves the research consent form from the patient if this has not already been returned

by post. This gives us permission to use tissue, data and images for research, teaching and audit purposes. The patient is then seen by a nurse, who takes a brief history, measures the visual acuity, measures the intraocular pressures and dilates both pupils, unless the tumour involves the iris.

Since January 2005, we have measured the visual acuity with a LogMAR chart, albeit with some teething problems as this examination is quite time-consuming and requires some expertise in computing the visual acuity.

### Next, the patient is seen by an SpR or oncology fellow, who:

- Takes a full ocular and systemic history, using a proforma in the casenotes. Details regarding mode of presentation and the referral pathway are also taken because we are auditing these aspects of care
- Performs a full ophthalmic examination, recording any findings by means of drawings
- Organises photography

### The patient is then seen by the photographer, who works full time in the ocular oncology service. She:

- Ensures that the research consent form is completed, in accordance with the patient's wishes
- Photographs the eye and tumour, according to the request form completed by the ophthalmologist
- Obtains a portrait of the patient, which is viewed by the specialist nurse at her computer terminal whenever the patient phones for advice



Fig. 5-1. Hostel accommodation at Royal Chambers



Fig. 5-2. Reception desk of outpatient clinic

**Next, the patient is seen by the consultant ocular oncologist, who:**

- Reviews the history and clinical findings
- Examines the patient with the slit-lamp and by ophthalmoscopy
- Performs ultrasonography
- Documents all findings, using the oncology proformas
- Counsels the patient about the diagnosis, prognosis, and any choice of treatment, also describing what each treatment involves. The most appropriate form of treatment is selected, in partnership with the patient, and taking into account the patient's own priorities. An audio-cassette tape-recording of the discussion is given to the patient, to ensure that nothing is forgotten
- Completes an estimates form in the presence of the patient, recording all predictions regarding survival, ocular conservation, preservation of vision, and complications. This is filed in the casenotes
- Computerises all relevant clinical data
- Dictates a report to the referring ophthalmologist, with copies to the GP, the patient, and, with the patient's permission, the optometrist. This report is faxed to the referring ophthalmologist and GP by the end of the next day

**The patient is then seen by the specialist ocular oncology nurse, who:**

- Ensures that the patient has understood all that was said by the consultant
- Answers all questions
- Identifies any special needs and concerns
- Organises accommodation for relatives, either at a nearby hotel or at Royal Chambers, which is part of the Royal Liverpool University Hospital

**The patient's care is then transferred to the ophthalmic sister, who:**

- Organises all relevant investigations. These include: full blood count, urea and electrolytes, liver function tests, electrocardiogram, chest x-ray if there is any lung disease, and liver ultrasonography if the uveal melanoma diameter exceeds 16 mm
- Arranges for the patient to be taken to Ward 8Y

As mentioned above, we have installed a kiosk in the clinic waiting area so that patients can learn more about uveal melanomas and their treatment, by means of an interactive program showing animated cartoons of various uveal melanomas and treatments.

At the end of the clinic, a multidisciplinary meeting is held to review all patients, discuss management decisions and resolve any organisational problems. This is attended by all the medical and nursing staff and by the oncology photographer, who shows images taken of each tumour, to enhance discussion.

**In the ward, the patient is:**

- Clerked-in by an ophthalmic SHO
- Reviewed by the oncology SpR, who completes all consent forms for surgery and pathology
- Assessed by the anaesthetist
- Visited by the specialist ocular oncology nurse



Fig. 5-3. Explaining condition to patient, with help of model eye, images, and audio-cassette tape-recorder

## SURGERY

On the day of surgery, the patient is visited by the oncology team at a pre-op ward round.

**The transfer to the surgical suite, the final pre-op checks, the operating procedures, and the immediate post-op care are performed in the standard fashion, with the following exceptions:**

- The eye to be operated on is examined, by binocular indirect ophthalmoscopy if necessary, and this is done after anaesthetizing and draping the patient
- Enucleation is performed with disposable instruments. A hydroxyapatite implant in vicryl mesh or an acrylic implant is used, depending on randomization if the patient has consented to participate in a prospective study currently in progress
- Specimens are taken for cytogenetic studies, if the patient has given consent for such investigations
- If the patient is treated with a radioactive plaque, a brachytherapy dosimetry form is completed and faxed to Clatterbridge Centre for Oncology so that the plaque removal time can be estimated
- If the patient is to receive proton beam radiotherapy, a proton beam form is completed, and this is sent to Clatterbridge Centre for Oncology together with colour photographs and ultrasound images so that the treatment plans can be prepared
- If the patient has an intraocular tumour biopsy with a 25-g vitreous cutter, or endoresection, or if a retinal tear occurs during trans-scleral local resection, appropriate surgery is performed by a vitreo-retinal surgeon

## POST-OPERATIVE CARE

**Post-operatively, the patient is:**

- Examined daily by an SHO, SpR or Fellow and the patient's care is reviewed daily by the consultant, specialist oncology nurse and ophthalmic nurse on a ward-round
- Visited by the health psychologist, who screens for psychological morbidity, organising appropriate care if necessary

## DISCHARGE

**At the time of discharge, the patient is given:**

- Any topical or systemic medications that need to be taken at home
- A note to take to the GP
- Instructions on how to remove and replace an artificial eye, if enucleation was performed
- An information sheet on post-operative care, convalescence, and on how to contact the specialist ocular oncology nurse
- A satisfaction questionnaire, to be completed anonymously and posted to our hospital using an addressed, stamped envelope provided
- An appointment at the referring hospital, this having been arranged by the ward clerk if it is necessary for the patient to be seen soon after discharge from our unit

## AFTER DISCHARGE FROM HOSPITAL

**After discharge from our hospital, the patient is:**

- Telephoned proactively by our specialist ocular oncology nurse within a week, to ensure that all is well and to deal with any problems
- Visited by a district nurse, if enucleation was performed, this having been arranged by our team.
- Telephoned by our health psychologist if this was pre-arranged at the time of the ward visit
- Sent an appointment to attend the clinic of our ocular oncologist at Clatterbridge Centre for Oncology, if cytogenetic studies show monosomy 3. The patient is advised to inform our oncologist if it is inconvenient or impractical to travel to the Wirral for this purpose, in which case the oncologist refers the patient to an oncologist at the patient's local hospital in addition to providing specialist advice

**There may be the following communications:**

- If a complication occurs, then a supplementary report is sent to the referring ophthalmologist, with copies to the patient and GP
- If pathology is performed, a copy of the report is sent to the referring ophthalmologist and GP, with a personalised letter written by the consultant explaining the significance of the results. A copy of this report is not sent to the patient unless it contains only good news, in which case the consultant arranges for an exception to be made
- If cytogenetic studies are undertaken, a copy of the results is sent to the referring ophthalmologist and GP, with an explanatory letter. If this report indicates an excellent prognosis for survival, a letter is sent to the patient by the consultant, with copies to the referring ophthalmologist and GP. The appointment at the oncology clinic at Clatterbridge Centre for Oncology is cancelled unless the patient is keen to discuss matters with an oncologist despite a good prognosis
- If the patient needs psychological care, our health psychologist writes to the GP to ask for this to be organised close to the patient's home
- If the patient has had enucleation and has agreed to participate in our randomised prospective study, a quality of life questionnaire is sent every six months

**FOLLOW-UP PROTOCOL**

**Our follow-up policy is as follows:**

- All patients with uveal melanoma are reviewed every six months for about six years and then annually until death, unless any problems require more frequent review
- All patients attending any of our clinics are seen by the consultant ocular oncologist at every visit
- Follow-up assessments are alternated between the Liverpool Ocular Oncology Centre and the referring hospital so that we can: (a) have enough space in our follow-up clinics to cope with approximately 250-300 new patients with uveal melanoma each year, every patient needing about two or three follow-up visits; (b) allow our consultant to see all patients; (c) enable referring consultants to provide continuity of care, so that no difficulties arise if the patient develops an urgent problem or when the

patient is eventually discharged from our care; and (d) enable junior staff at referring hospitals to gain experience in the follow-up care of patients treated for uveal melanoma

- Patients are discharged permanently from our ocular oncology service only when the chances of local tumour recurrence are estimated to be about one percent
- Patients are seen without delay at our centre at any time if the referring ophthalmologist ever has any concerns about recurrence or any other problems

**FOLLOW-UP AT LOCAL HOSPITAL**

Arrangements are made for patients to be reviewed at their local hospital approximately one week after any intraocular procedure (e.g. trans-scleral local resection, vitrectomy, intraocular triamcinolone injection), one month after extraocular treatment (e.g. plaque radiotherapy, enucleation, conjunctival tumour excision) and eight weeks after proton beam radiotherapy.

**In the immediate post-operative period, the main complications that need to be excluded are:**

- Raised intraocular pressure after vitrectomy, intravitreal steroid injection, or topical steroid therapy
- Rhegmatogenous retinal detachment after local resection of an intraocular tumour
- Endophthalmitis after any intraocular procedure
- Orbital cellulitis after enucleation
- Hypotony after iridocyclectomy or cyclochoroidectomy
- Uveal effusion after plaque radiotherapy
- Severe exudative retinal detachment after radiotherapy
- Corneal dellen after treatment of a medial tumour
- Diplopia after extraocular muscle disinsertion
- Allergy to any topical medications
- Adverse reactions to any oral medications

**In the long term, the main complications include:**

- Local tumour recurrence. This is best identified by comparing ophthalmoscopic appearances with baseline colour photographs. Ultrasonography would be ideal, allowing detection of increasing thickness. The measurement should be taken from the internal scleral surface, taking account of any retinal detachment over the tumour. Any apparent increase in thickness not exceeding 0.5 mm should be regarded as measurement variation and the examination should be repeated several weeks or months later. Ultrasonography is also useful for detecting extraocular recurrence. Tumour can recur many years after treatment, which is why surveillance needs to be life-long
- Regional metastases after treatment of a conjunctival tumour should be excluded by palpating local lymph nodes at every visit
- Maculopathy after radiotherapy. Oedema can be treated by administering transpupillary thermotherapy to the tumour or intra-vitreous triamcinolone. The results are likely to be better if the oedema is not prolonged. Cellophane maculopathy can be treated surgically
- Cataract is treated in the usual manner. After cyclectomy, the lens may be unstable so that an intracapsular ring may be indicated. If there is a large iris defect, it might be worth considering an artificial iris
- Exudative retinal detachment after brachytherapy or proton beam radiotherapy usually resolves spontaneously after a few months but may cause neovascular glaucoma if prolonged or severe. This can be treated successfully by removing the irradiated tumour
- Glaucoma usually responds to topical medical therapy. If secondary to tumour invasion of the angle, drainage surgery should be safe after radiotherapy but is best avoided in case there is any active residual tumour. Cyclodestructive procedures are therefore preferable. After radiotherapy, neovascular glaucoma secondary to exudative retinal detachment may regress if the detachment is treated successfully
- Diplopia, if persistent, can be treated with prisms or appropriate extraocular muscle surgery. If strabismus occurs after trans-scleral local resection, muscle surgery may be associated with

an increased risk of perforation in the region of the lamellar scleral flap. You may wish to discuss the case with us or refer the patient back to our centre for appropriate surgery using special techniques we have developed

- Metastatic disease after treatment of uveal melanoma. Counselling and screening are best undertaken by the oncologist who would treat the patient should this complication arise. It may be helpful for the oncologist to liaise with our centre in case we are able to offer specialist advice or to enter the patient into a clinical trial

**FEEDBACK****We obtain the following feedback:**

- A copy of any report sent by the referring ophthalmologist to the general practitioner after each clinic. After being read by the consultant, who takes any appropriate action and answers any questions, the letter is passed on to the data manager, who updates the computerised database
- Photocopies of casenotes from referring hospital are requested from time to time (i.e. once every few years) when we are performing an in-depth evaluation of a particular form of treatment. Patients are informed of this practice and we obtain specific consent for this to be done. We request photocopies of notes so that this work can be done by hospital secretaries as part of their normal duties. Forms and questionnaires are avoided because these would need to be completed by medical staff in referring hospitals, perhaps after hours. The photocopies are received by our data manager who is expert at retrieving the relevant information (i.e. visual acuity, cataract, etc). No judgements, comments or assessments, formal or informal, are ever made about quality of care or adequacy of documentation, with the confidentiality of practitioners being respected as carefully as that of patients
- Phone calls from patients. Several patients regularly telephone our specialist oncology nurse with questions or for reassurance, sometimes after being seen at their local hospital. If there seems to be a problem, we may urgently review the patient at our follow-up clinic

- Automatic notification from the NHS Cancer Registry of the date and cause of death of any deceased patients treated for uveal melanoma at our centre. This is possible because we notify the Cancer Registry of each new patient with melanoma, also providing the NHS number so that the patient can be flagged
- Quality of life questionnaires returned by all patients with uveal melanoma on the anniversary of their initial treatment. This is done with ethical committee approval, with informed consent from each patient, and in collaboration with our health psychologist and the professor of psychology at the University of Liverpool. The data are computerised for statistical analysis by co-workers in the Department of Clinical Engineering. This project is undertaken by our compliance officer so that in future we can comply better with patient's needs and wishes
- Consent forms from all patients previously treated for uveal melanoma, giving permission for: the use of images, data and tissues for research, teaching and audit; consent for participation in quality of life studies; and interest in receiving an annual newsletter, currently in preparation. At present, we are obtaining suggestions from patients as to what should be included in this newsletter

A detailed ocular oncology protocol describes the care pathway and lists all the duties of each member of the team together with instructions on how these duties should be undertaken.

Our policies are all reviewed by the National Specialist Commissioning Advisory Group, which funds our service.

## MULTIDISCIPLINARY AND OPERATIONAL REVIEW MEETINGS

### These include:

- New patient MDT meeting, at the end of each initial assessment clinic, as mentioned above
- Pathology MDT meetings once or twice a month, to review all histology
- Radiotherapy MDT meetings once every one or two months, to review any failures of local tumour control or any other complications
- Oncology MDT meetings to review policy and to discuss any adverse events
- Cytogenetic MDT meetings to review policy and discuss any deaths from metastatic disease in the absence of monosomy 3
- An annual MDT involving all individuals participating in the oncology service in any way. This includes didactic element and all staff of St Paul's Eye Unit are invited to attend

# AUDIT AND RESEARCH

Audit is an integral part of our work. Our aim is to audit all outcomes of every patient continuously and to perform regular statistical analyses according to relevant baseline variables following correct protocols.

We tend to publish the results of most of our audits in leading journals. We are planning to increase transparency by also making our results widely available on the Internet.

There is some overlap between our audit and research so that both these activities are considered in this chapter.

## CONSENT

**Although ethical committee approval and patient consent have not previously been required for audit, the legal situation may change and we therefore obtain as much consent and from as many patients as possible. We have appointed a compliance officer specifically for this purpose. The roles of this officer are to:**

- Obtain consent from all current and previously treated patients for the use of tissues, data and images for research, teaching and audit
- Obtain ethical committee approval for any studies we are undertaking
- Obtain approval from the hospital R&D department for all our studies
- Maintain a register of all our studies

## STUDIES

**We are undertaking several studies, some of which include:**

- An audit of mode of presentation of patients with uveal melanoma in the UK. The aim of this study is to highlight any procedural failures and to demonstrate how outcomes are influenced by early detection. To date, we have data on well over 1,500 patients with uveal melanoma. Interim analyses show that about 40 percent of all patients with uveal melanoma are asymptomatic when their tumour is detected by an optometrist. These patients do best in terms of ocular and visual preservation. About 20 percent of patients with symptomatic

choroidal melanoma report that their tumour was missed when they first presented. Median time to treatment is much longer if the patient is referred by the optometrist via the general practitioner instead of directly to the hospital

- An audit of diagnostic accuracy suggests that many patients are referred to an oncology centre with an uncertain or incorrect diagnosis. This suggests that the one percent mis-diagnosis rate reported by the Collaborative Ocular Melanoma Study does not reflect the real life situation, when there are no exclusion criteria.
- An audit of plaque radiotherapy of choroidal melanoma indicates a very high rate of local tumour control, which is achieved despite placing the plaque eccentrically in relation to the tumour, without any physical safety margin posteriorly.
- An audit of proton beam radiotherapy of choroidal melanoma shows high rates of visual loss despite low doses of radiation being delivered to optic disc and macula.

This study demonstrates that visual loss often occurs as a result of exudation from the irradiated tumour, which can be treated by administering transpupillary thermotherapy to the irradiated tumour or by intra-vitreous steroid injection

- An audit of proton beam radiotherapy of iris melanoma shows good results, the main side-effect being cataract, which is easily treated. Glaucoma can be a problem if there is extensive angle involvement by tumour or macrophages. Local tumour recurrence can occur if these two cell types are not correctly differentiated pre-operatively, highlighting the need for biopsy
- An audit of local resection indicates that ocular conservation can be achieved in about 90 percent of eyes with vision depending on size and location of tumour. The main complication is local tumour recurrence, which is prevented by adjunctive brachytherapy in most patients. Rhegmatogenous retinal detachment has become rare with better avoidance of retinal tears and immediate vitreoretinal surgery when a break does occur
- We are currently auditing local tumour recurrence after conservative treatment of uveal melanoma
- An audit of cytogenetic studies of uveal melanoma

in patients treated by local resection or enucleation indicates that loss of chromosome 3 and gains in chromosome 8 are associated with a reduction in the five-year survival from about 95 percent to less than 50 percent. Chromosome 6 abnormalities also influence prognosis and abnormalities in several parts of this chromosome are being correlated with survival. At present, we are waiting for data to mature before publishing our results

- We are also performing molecular genetic studies of uveal melanoma, using microarrays and other methods in the hope of improving our understanding of mechanisms for metastasis
- The psychological impact of cytogenetic studies is being evaluated by our health psychologist, with ethical committee approval. She is visiting patients in their homes to obtain a true impression of their feelings and how these are affected by good or bad cytogenetic results
- The quality of life of all patients treated for uveal melanoma is being measured annually. After a few years we should have enough data to advise patients not only what the surgical results will be but also how they are likely to feel. This should inform decision making, allowing choice to be tailored to age, gender and other important factors
- In collaboration with the Department of Clinical Engineering at the Royal Liverpool University Hospital, we have developed neural network models for predicting survival after treatment of uveal melanoma and are now extending this work to predict other outcomes and to develop new prognostic models in collaboration with other centres
- Also in collaboration with the Department of Clinical Engineering, we have developed geoconda.com, an Internet environment for multicentre research in ocular oncology. We have used this successfully in a multicentre evaluation of statistical methods for evaluating survival after treatment of uveal melanoma in Liverpool. We are establishing a multicentre audit of ocular and systemic outcomes after treatment of uveal melanoma. This website is to be extended to allow data on the same patient from different sources to be merged, therefore creating opportunities for multicentre multidisciplinary virtual meetings, case conferences, and preparation of an internet atlas of ocular oncology.

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PATIENT SATISFACTION SURVEY (MARCH TO NOVEMBER 2005)

	Yes (completely/ definitely/always)	Yes (sometimes/to some extent)	No	Total	No fears No pain	No answer
Q1 Consultant answered questions adequately?	97%	3%	0%	96	4	
Q2 Specialist Nurse answered questions adequately?	97%	2%	1%	98	2	
Q3 Consultant addressed fears?	93%	7%	0%	86	12	2
Q4 Specialist Nurse addressed fears?	89%	8%	3%	85	15	
Q5 Nurse addressed fears?	74%	17%	9%	76	21	3
Q6 Consultant explained treatment?	96%	4%	0%	99	1	
Q7 Adequate advice from secretary?	74%	11%	15%	72	26	2
Q8 Doctors talked in front of you as if you were not there?	3%	4%	93%	93	7	
Q9 Clear understanding after consultant visit?	77%	22%	1%	100	0	
Q10 Feel you could ask for information?	89%	9%	2%	100	0	
Q11 Wanted more involvement with decisions?	18%	10%	72%	80	17	3
Q12 Treated with respect during stay?	92%	7%	1%	100	0	
Q13 Treated with dignity during stay?	92%	7%	1%	99	1	
Q14 Experienced pain?	13%	56%	31%	98	1	1
Q15 Hospital staff helped to control pain?	88%	11%	1%	73	20	7
Q16 Friends/family spoke to doctor?	78%	18%	4%	85	14	1
Q17 Doctor gave adequate recovery information to family and friends?	81%	15%	4%	88	11	1
Q18 Nurse gave adequate recovery information to family and friends?	79%	15%	6%	85	13	2
Q19 Staff explained purpose of treatment?	83%	13%	4%	98	0	2
Q20 Staff explained side-effects of treatment?	61%	17%	22%	88	11	1
Q21 Information received about danger signals at home?	45%	23%	32%	87	12	1

(All patients discharged from ward were given satisfaction questionnaires, which were completed and returned anonymously using stamped and self-addressed envelopes.)

# TEACHING

In view of the rarity of ocular tumours, we feel it is our duty to document as much clinical information as possible and to share our knowledge with general ophthalmologists and ocular oncologists around the world.

## We have therefore created protocols for:

- Obtaining patient consent for the use of images in publications, whether these are in textbooks, journals or electronic resources (such as CD ROM or Internet)
- Maintaining an ocular oncology database
- Maintaining photographic archives

## Our teaching occurs by means of:

- Oral presentations at departmental meetings as well as national and international conferences
- Published case presentations
- Review articles in journals
- Chapters in textbooks
- Ophthalmic textbooks

We hope to establish an internet atlas of ocular oncology as an aid to diagnosis and to enable non-specialists to predict what treatment their patient might receive and what outcomes could be expected.

## We also teach individuals by receiving:

- Observers, usually from overseas, who come to observe our clinics and surgical procedures. Such visitors are usually fully trained and distinguished ocular oncologists
- Fellows, who work at SpR level for six to 12 months, receiving a salary either from our department or from other sources
- Medical students, who wish to gain an overview of a specialist ophthalmic service and of ophthalmology in general.

## Other forms of teaching include:

- Ensuring that the report to the referring ophthalmologist is written by the consultant and that the rationale for establishing a diagnosis or selecting a treatment is explained
- Copying reports on all new patients to the optometrist, if permission is granted by the patient, so that feedback is provided

- Alternating follow-up visits with the referring hospital, so that staff at that hospital can become familiar with the patient's condition by the time that patient is discharged from the ocular oncology service
- Explaining pathology and cytogenetics reports so that this experience is shared with referring ophthalmologists and their trainees

## ORAL PRESENTATIONS IN 2005

### Invited lectures at conferences

- RNIB, London, UK (April 2005): Diagnosis and treatment of rare diseases: melanoma
- 7th International Vitreoretinal Meeting, Parma (April 2005): Surgical management of uveal melanoma
- ARVO, Fort Lauderdale (May 2005): Geoconda.com: an internet environment for multicentre research in ocular oncology
- Barraquer Institute Conference, Barcelona (May 2005)
- International Congress of Ocular Oncology, Vancouver (Sept 2005) Prospects for Change in Uveal Melanoma Management (Keynote lecture) and Cytogenetic Studies on Uveal Melanoma
- Spanish Society of Ophthalmology Congress, Zaragoza (Sept 2005)
- European Society of Ophthalmology, Berlin, Germany (Sept 2005): How do I use molecular genetic information as an ophthalmologist? And Diagnosis of intraocular tumours
- EVER Vilamoura, Portugal (Oct 2005): Choroidal tumour biopsy with 25-gauge vitreous cutter.
- ECCO, Paris, France (Oct 2005): Current management of uveal melaoma
- Advanced Retinal Therapy Conference, Vienna, Austria (Nov 2005). Surgical resection of uveal melanoma

### Submitted presentations at conferences

- Macula Society Conference, Key Biscayne, US (Feb 2005): Clinical cytogenetics of uveal melanoma
- International Congress of Ocular Oncology (Sept 2005): 'Geoconda.com: an internet environment for multicentre ocular oncology research', and 'A Ciliary Body Tumour in a Teenager'

**Invited presentations at departmental meetings**

- Department of Ophthalmology, Redhill (Apr 2005):  
Management of uveal melanoma.
- Nice Ophthalmic Group Meeting (Jun 2005):  
Management of uveal melanoma
- Grand Round, Royal Liverpool University Hospital  
(Sept 2005): Radiotherapy of uveal melanoma
- Wirral Optometry Group Meeting, Bromborough  
(Nov 2005): Management of uveal melanoma

# FREQUENTLY-ASKED QUESTIONS

## What information should we give when we refer a patient to an oncology centre?

### We need:

- The patient's full demographic details (date of birth, gender, etc), including address and any phone numbers (home, work and mobile)
- A description of the ocular and general condition of the patient, including the suspected diagnosis and the approximate size of the tumour
- The patient's NHS number if this is known.
- The GP's full name and address as well as the fax number and telephone numbers if available
- Any special requirements (e.g. interpreter, wheelchair, etc)
- Any other relevant information (e.g. dates of any impending holidays booked)

## Which patients should not be referred to Liverpool?

### Patients should not be referred for:

- CHRPE
- Simple naevi that are flat or only minimally elevated with drusen
- Eyelid tumours
- Orbital tumours

## How should we refer the patient?

Patients can be referred by mail, phone or fax, preferably by more than one method for safety reasons.

## Where can we refer our patients?

### There are four designated adult ocular oncology centres in the UK, and these are:

- Gartnavel General Hospital, Glasgow
- Royal Liverpool University Hospital, Liverpool
- St Bartholomew's Hospital and Moorfields Eye Hospital, London
- Royal Hallamshire Hospital, Sheffield.

You can send your patient to any of these centres; however, referral of Scottish patients to England requires prior approval from NSD Scotland.

## What investigations should we perform before referring the patient?

There is no need to perform any tests. In any case, referral should not be delayed by any investigations. Biopsy of conjunctival tumours is not advised (except for primary acquired melanosis).

## Can I phone before I refer the patient and whom should I speak to?

You can certainly phone with any questions. The secretary can usually answer these, but if not she will contact the consultant or arrange a call back.

## I am worried about shared care in case I miss local tumour recurrence after treatment of uveal melanoma?

Patients are discharged from the ocular oncology service only when the chances of local tumour recurrence are in the region of one percent.

## How dangerous is local tumour recurrence after treatment of uveal melanoma?

Local tumour recurrence is indeed associated with increased mortality, but it is not known whether this is because the recurrence is the source of the metastasis or whether the recurrence is merely an indicator of increased malignancy of the primary tumour.

## How safe is it to observe a patient with an indeterminate melanocytic choroidal tumour?

It is currently accepted practice to delay treatment of a 'suspicious naevus' until growth is documented. However, it is not known when metastasis starts to occur and therefore the risk involved in delaying treatment is uncertain. Patients should be advised about this.

## Is it not safer to treat uveal melanoma by enucleation?

There is no evidence to suggest that enucleation confers any advantage in survival probability as compared with conservative methods of treatment.

## Is it ethical to inform patients of a high risk of metastatic disease, when there is no effective treatment?

Feedback we have received so far suggests that patients wish to know their prognosis even if this is poor. There are several patients who have told us that this knowledge helped them to organise their affairs while they still felt well. Our health psychologist is auditing this practice and we are also receiving advice from a professional medical ethicist, who has recently been recruited onto our team.

**Should patients with uveal melanoma be screened for metastatic disease? If so, how? What is the benefit?**

If screening is performed, asymptomatic spread is most likely to be detected by liver ultrasonography and biochemical liver function tests performed every six to 12 months. There is no consensus about which patient should be screened and how long such screening should be continued.

There is also controversy about screening for a disease that is only rarely treatable and when any benefit is usually short-lived. For all these reasons, we feel decisions regarding any screening should be made by the oncologist who would be treating any metastases if these were to develop.

**What precautions are necessary when administering topical chemotherapy?**

Patients are provided with: disposable gloves, which should be worn when drops are administered; a disposable waste-container, for used gloves and empty bottles of chemotherapy drops; and Vaseline, for protecting the lower eyelid. They are shown how to instil the drops safely and how to store the medication out of the reach of children.

They are also instructed to return all waste to our hospital, or to their GP clinic, or to their local hospital pharmacy for safe disposal. We do not use punctal plugs, because the drops may prevent tumor recurrence in the nasolacrimal ducts and because any punctal stenosis should be readily treatable.

Preservative-free mitomycin C or 5-FU need to be prepared just before administration so that patients usually need to return to our hospital for drops. Topical steroids may be needed if there is excessive discomfort.

**Is it safe for women to receive hormone replacement therapy after treatment of uveal melanoma?**

To our knowledge, a previous history of uveal melanoma is not a contraindication to hormone replacement therapy.

**Why does it take so long for letters to reach us from the oncology centre?**

As a rule, outpatient clinic letters are dictated before the next patient is seen and mailed within a day, unless there are any errors requiring the letter to be re-typed.

Previously, discharge letters on inpatients were dictated when the patient was still in the operating theatre and mailed one day later; however, feedback suggested that these letters were taking some time to be received. We now dictate the discharge letter as soon as the patient is admitted and fax it by the end of the next working day.

**What can I do to help?**

**To help us, the referring ophthalmologist can:**

- Refer the patient promptly
- Avoid any surgery on nodular conjunctival tumours
- Send baseline photographs if the tumour has been observed to grow over time
- Inform the patient of the suspected diagnosis before referral. Some patients get upset if they have not been advised of the suspected diagnosis by their consultant or optometrist
- Advise the patient what to do if an appointment letter or phone call from the oncology service is not received within two weeks
- Reassure the patient if the tumour is considered to be benign
- Participate in shared care, alternating follow-up visits with our centre until we consider it safe to discharge the patient from our hospital
- Send us copies of any clinic or discharge letters mailed to the GP
- Inform us if the patient develops any complications or if the patient has died
- Send us copies of casenotes upon request. This happens rarely, only every few years
- Complete and return any questionnaires surveying satisfaction of the referring ophthalmologist with our service. This questionnaire is not sent more than once a year
- Inform us of any problems or complaints so that these can be dealt with promptly

**Please send us more questions and suggestions so that this guide can be improved.**

# FURTHER INFORMATION

## PERSONAL COMMUNICATION

### You can contact us by:

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Fax: **+44 (0) 151 706 5436**

e-mail: **Bertil@Damato.co.uk**

## TEXTBOOKS

- Atlas of Intraocular Tumors and Atlas of Eyelid and Conjunctival Tumors. JA Shields & CL Shields. Lippincott Williams & Wilkins. Philadelphia, 1999.
- Ocular Tumours. Diagnosis and Treatment. B Damato. Butterworth Henemann, Oxford, 2000.
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- Diseases of the Ocular Fundus. J Kanski, S Milewski, B Damato, V Tanner. Elsevier Mosby, Edinburgh, 2005.
- Ophthalmology Clinics of North America. Ed: Singh AD. Elsevier Saunders. Philadelphia. 2005.
- Retina. Fourth Edition. Ed: SJ Ryan. Volume 1. Tumors. Ed: AP Schachat. Elsevier Mosby, 2006.

## INTERNET SOURCES

### Pubmed

[www.pubmed.com](http://www.pubmed.com)

### CancerBACUP

[www.cancerbacup.org.uk/Home](http://www.cancerbacup.org.uk/Home)

### NSCAG

[www.advisorybodies.doh.gov.uk/NSCAG/](http://www.advisorybodies.doh.gov.uk/NSCAG/)

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