Clinical Ophthalmic Oncology

Uveal Tumors

Bertil E. Damato
Arun D. Singh
Editors

Third Edition

Springer

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Preface

Ophthalmic tumors are rare and diverse so that their diagnosis can be quite complex. Treatment usually requires special expertise and equipment and, in many instances, is controversial. The field is advancing rapidly, because of accelerating progress in tumor biology, pharmacology, and instrumentation. Increasingly, the care for patients with an ocular or adnexal tumor is provided by a multidisciplinary team, consisting of ocular oncologists, general oncologists, radiotherapists, pathologists, psychologists, and other specialists.

For all these reasons, we felt that there was a need for the new edition of the textbook providing a balanced view of current clinical practice. Although each section of *Clinical Ophthalmic Oncology* now represents a stand-alone volume, each chapter has a similar layout with boxes that highlight the key features, tables that provide comparison, and flow diagrams that outline therapeutic approaches.

The enormous task of editing a multiauthor, multivolume textbook could not have been possible without the support and guidance by the staff at Springer: Caitlin Prim, Melanie Zerah, ArulRonika Pathinathan, and Karthik Rajasekar. Michael D. Sova kept the pressure on to meet the production deadlines.

It is our sincere hope that our efforts will meet the high expectation of the readers.

Oxford, UK — Bertil E. Damato
Cleveland, OH, USA — Arun D. Singh

Acknowledgments

To my family, Frankanne, Erika, Stephen, and Anna (BED)

To my parents, who educated me beyond their means, and my wife, Annapurna, and my children, Nakul and Rahul, who make all my efforts worthwhile (ADS)

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1 Uveal Tumors: Examination Techniques

Bertil E. Damato and Iwona Rospond-Kubiak

Introduction

This chapter highlights procedures that are specific to the assessment of a patient with a uveal tumor. It is assumed that a full ophthalmic and systemic history is routinely obtained in all patients in addition to complete examination of both eyes and appropriate systemic assessment, consisting of clinically relevant ancillary investigations.

History Taking

Initial Assessment

The past medical 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 tumor, such as melanoma and hemangioma, because dual pathology is not uncommon. The history 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 hemangioma in whom visual loss is irreversible if long-standing.

Follow-Up

Routine use of a questionnaire ensures that at every follow-up visit, each patient is asked all relevant questions about general health, visual symptoms, ocular discomfort, and concerns about possible ocular complications and survival.

Visual Acuity

If possible, the visual acuity should be measured using a LogMAR chart, which overcomes the limitations of the Snellen test, also facilitating statistical analysis of vision in any outcomes analysis [1]. If central vision is lost, the eccentric visual acuity should be measured using the optotype and, if necessary, finger counting before checking for hand movement vision.

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Slit-Lamp Examination

It is necessary to define the primary tumor, recognizing any secondary effects, predisposing factors, and concurrent disease (Box 1.1):

(i) Site of origin (iris, ciliary body, choroid).
(ii) Location (superior, supero-nasal, nasal, etc.).
(iii) Circumferential spread, ideally in clock minutes in a clockwise direction (e.g., 5–30 or 55–5). This is easier than using degrees and more precise than clock hours. For iris tumors, there may be a scope for recording circumferential spread at pupil margin as well as the midperipheral and peripheral iris.
(iv) Posterior margin (pars plicata, iris surface).
(v) Anterior margin (iris surface, angle, cornea).
(vi) Consistency (solid, cystic, multicystic).
(vii) Shape (flat, dome, multinodular).
(viii) Margins (diffuse, discrete).
(ix) Color (pink, white, yellow, red, orange, tan, brown, black, etc.).
(x) Vascularity (present or absent).
(xi) Seeding (across iris, into angle, vitreous).
(xii) Angle involvement (in clock minutes). The first author (BD) finds it useful to describe the angle in each clock hour as normal, scanty pigment dusting, dense pigment dusting, flat confluent pigment, bulky confluent pigment, tumor, and uncertain (because of closed angle or hyphema) .
(xiii) Extraocular spread (absent, nodular, diffuse).
(xiv) Longitudinal and transverse basal dimensions, using the measure on the slit lamp.
(xv) Secondary effects (dilated episcleral vessels, band keratopathy, glaucoma, hyphema, ectropion uveae and pupillary peaking, iris cyst formation, and lens abnormality such as cataract, deformity, and subluxation).
(xvi) Predisposing factors (ocular or oculodermal melanocytosis, Sturge-Weber syndrome, and other vascular malformations).

Box 1.1. Examination Techniques for Tumors

- History taking, slit-lamp examination, and ophthalmoscopy.
- Drawings complement photography, especially with peripheral tumors.
- Tumor dimensions can be estimated using charts and ophthalmoscopically.
- Three-mirror examination is useful in selected cases.
- Transillumination gives an approximate indication of tumor extent.

The author (BD) has designed a diagram to facilitate documentation of slit-lamp findings (Fig. 1.1). Although intended primarily for conjunctival tumors, it is useful also with iris and ciliary body tumors.

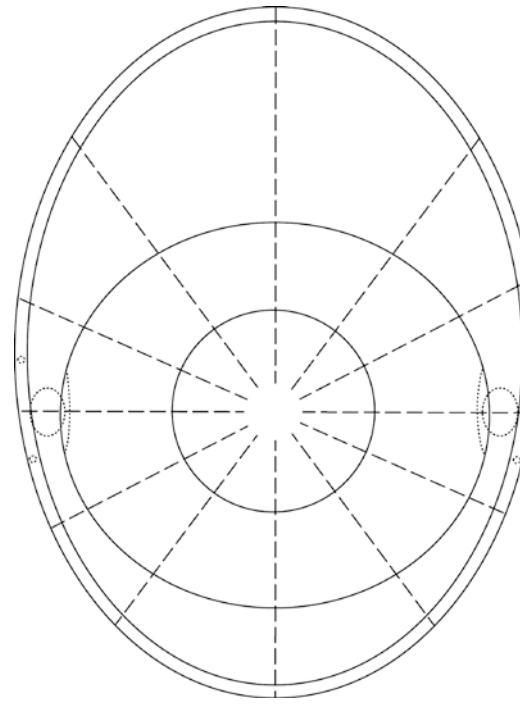

Fig. 1.1 Template for documenting slit-lamp findings

Indirect Ophthalmoscopy

It is essential to examine the entire fundus, with indentation if necessary, to identify any other pathology. Both eyes should be examined, ideally with mydriasis. The first author (BD) has devised the mnemonic, MELANOMA, to alert the clinician to the presence of an intraocular tumor in situations where the pupils are not routinely dilated (Box 1.2).

Box 1.2. Symptoms and Signs Indicating Presence of an Intraocular Tumor

- ***M***elanoma or other tumor visible externally in iris or episclera
- ***E***ccentric visual phenomena, such as photopsia, floaters, and field loss
- ***L***ens abnormalities, such as cataract, astigmatism, and coloboma
- ***A***fferent pupillary defect, mostly caused by secondary retinal detachment
- ***N***o optical correction with spectacles because of blurring or metamorphopsia
- ***O***cular hypertension, especially if asymmetrical
- ***M***elanocytosis, predisposing to melanoma
- ***A***symmetrical episcleral vessels, indicating a ciliary body tumor

It is necessary to describe the primary tumor, any secondary effects, and any predisposing factors as follows:

(i) Tissue of origin (choroid, retina, retinal pigment epithelium)
(ii) Quadrant (superotemporal, superior, superonasal, etc.)
(iii) Shape (flat, dome, collar stud)
(iv) Margins (discrete, diffuse)
(v) Color (pink, white, yellow, red, orange, tan, brown, black, etc.)
(vi) Vascularity (vascular, avascular)
(vii) Posterior extent, including distances to optic disc margin and fovea (disc diameters or mm)
(viii) Anterior extent (post-equatorial, pre-equatorial, pars plana, pars plicata, etc.)
(ix) Circumferential involvement of disc, ciliary body, and perhaps choroid (in clock minutes)
(x) Internal spread (subretinal space, retina, vitreous)
(xi) Secondary effects (RPE changes such as drusen and orange pigment over the tumor, RPE changes adjacent to the tumor, exudative retinal detachment, and hemorrhage)
(xii) Predisposing factors (ocular melanocytosis, melanocytoma, diffuse choroidal hemangioma)

Fundus Drawing

Fundus drawings complement photography in several ways, for example, allowing important features to be highlighted by means of notes and markers. The technique has been described in detail elsewhere (Fig. 1.2) [2].

A. Ask the patient to lie supine on a couch or in a reclining chair.
B. Stand at the head end of the patient and place the retinal chart on a tray next to the patient's head. The top of the chart should be facing toward the patient's feet. You should be able to move around so as to position yourself directly opposite the retinal quadrant being examined.
C. Hold the indirect lens in the nondominant hand and a pencil in your dominant hand.
D. Draw symbols for the optic disc and fovea, and then look at the fundus and rotate the drawing pad so that the optic disc and fovea are aligned in the same way as the fundus image.
E. Identify the meridians, in clock hours, of the two lateral margins of the tumor, in relation to disc or fovea, and draw these lines on the chart.
F. Estimate the distance between posterior tumor margin and disc or fovea and mark that point on the chart.
G. Estimate the location of the anterior tumor margin in relation to equator or ora serrata and mark that point on the chart.
H. Draw the profile of the tumor, using the marks already on the chart as guides.
I. Starting at the tumor and working backward toward the optic disc, draw the major retinal blood vessels, placing conspicuous bifurca-

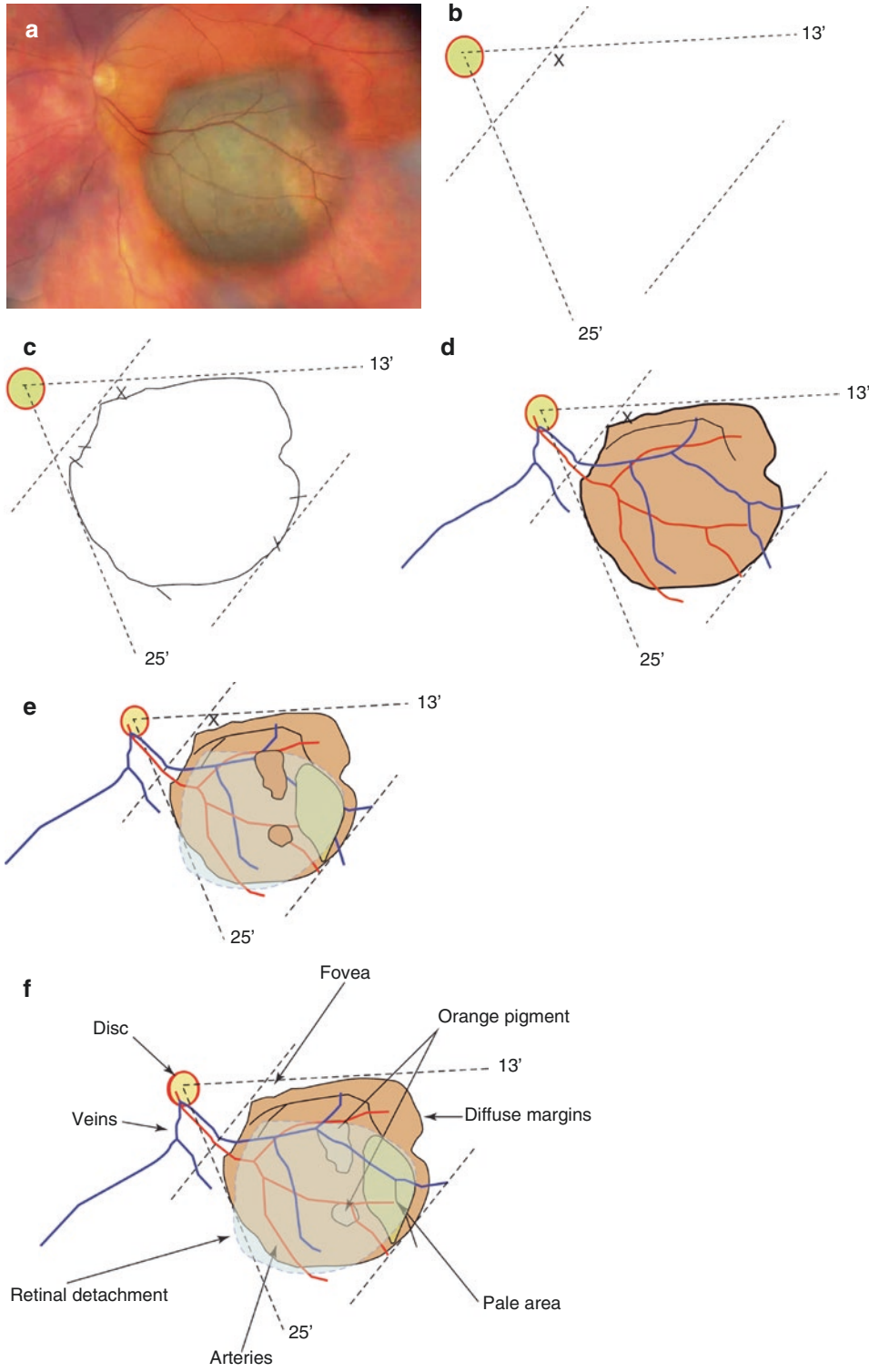

Fig. 1.2 Drawing a choroidal tumor. Color photograph (**a**). Locating tumor margins with respect to disc and fovea (**b**), delineating tumor margins (**c**), drawing vascular details (**d**), adding tumor features (**e**), and annotations (**f**). (Reprinted from Damato [2]. With permission from Elsevier)

tions and crossings in their correct positions in relation to tumor margins.

J. Fill in details, such as texture, tumor vessels, RPE changes, hemorrhages, exudates, and retinal detachment.

K. Ensure that the patient's name and hospital number, the date of the examination, and your signature have all been documented. (Fig. 1.3a, b) shows an example of how fundus lesions are documented.

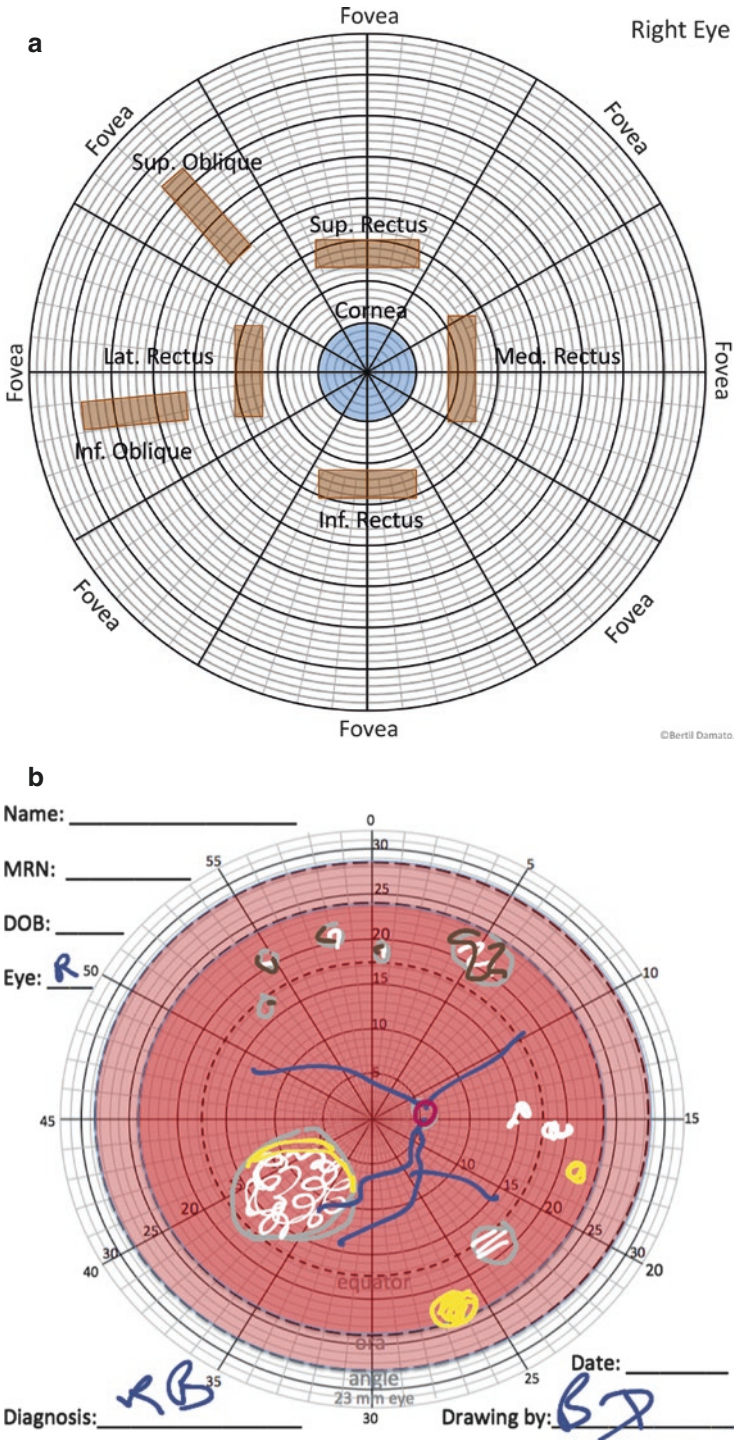

Fig. 1.3 Chart showing outer ocular surface, designed to help plan insertion of radioactive plaque or tantalum markers for the treatment of posterior segment tumors (**a**). The fovea is represented by a large ring, its distance from the limbus varying with axial length. Chart designed by the first author with the fundus demarcated circumferentially in clock minutes and radially in millimeters (**b**). The use of this chart as a template on an electronic tablet allows digital drawings to be prepared accurately and ergonomically, also facilitating transmission by the Internet and uploading onto electronic records

Estimation of Intraocular Tumor Basal Dimensions

Schematic diagrams have been prepared to facilitate estimation of ocular dimensions on clinical examination [2]. We have developed a system for drawing fundus diagrams on an iPad using a template we developed to enhance accuracy (Fig. 1.3b). The preparation of digital drawings with inexpensive programs is ergonomic, especially in a dark room, and allows easy modification and uploading onto electronic records. Basal dimensions of intraocular tumors can also be measured by indirect ophthalmoscopy. The chord length tumor basal diameters (anteroposterior or longitudinal and circumferential or latitudinal) are estimated while performing indirect ophthalmoscopy by assessing the proportion of a specific condensing lens field that is filled by the tumor's image. During this assessment, a 20D lens is considered to have a field diameter of approximately 12 mm, whereas a 28D lens is regarded to have a field diameter of 13 mm. For example, a tumor which fills one-half of the 20D lens field would be judged to have a diameter of approximately 6 mm, while a tumor filling two-thirds of a 28D lens field would be considered to be about 8.5 mm in diameter. Tumor dimensions can also be measured by ultrasonography, as described elsewhere.

Three-Mirror Examination

Three-mirror examination is necessary to:

A. Indentify the cause of raised intraocular pressure.
B. Determine whether a lesion behind the iris is solid or cystic.
C. Find a small, retinal angioma.
D. Determine the anterior extent of a pre-equatorial tumor.
E. Measure the circumferential extent of ciliary body or angle involvement by a tumor, aligning in turn each lateral tumor margin with the center of the mirror.

Transillumination

Transillumination can be used to detect or locate tumor margins. In general, pigmented tumors and intraocular hemorrhage block transmission of light. It must be realized that not all pigmented tumors are melanoma and, conversely, not all melanomas are pigmented. Various techniques of transillumination include (Fig. 1.4):

A. Trans-pupillary, placing the illuminator on the cornea. Care must be taken not to overestimate posterior extension because of an oblique shadow cast by a thick tumor.
B. Trans-ocular, with a right-angled transilluminator on the globe directly opposite to the tumor. This is less convenient than trans-pupillary transillumination but more accurate. This is the first author's preferred technique when identifying the lateral and posterior tumor margins intraoperatively, using a 20-gauge vitrectomy illuminator, which is bent 90°.
C. Trans-scleral, with the light source on the sclera over the tumor. This only determines whether or not the tumor transmits light.

Transillumination is also useful for identifying scleral necrosis and iris atrophy.

Color Photography

Color photography is useful for documenting the appearances of the tumor and other parts of the eye. The tumor color can vary greatly between cameras. For example, with the Optos camera, amelanotic metastases and hemangiomas may falsely appear pigmented (Figs. 1.5 and 1.6) [3, 4]. Tumor diagnosis should therefore not be based on color photographs.

Photography also defines the tumor extent in relation to adjacent landmarks, such as retinal blood vessels and pupil margin. Sequential photography is usually helpful in detecting tumor growth over time (Fig. 1.7). False impressions of growth can arise, however, as a result of inconsis-

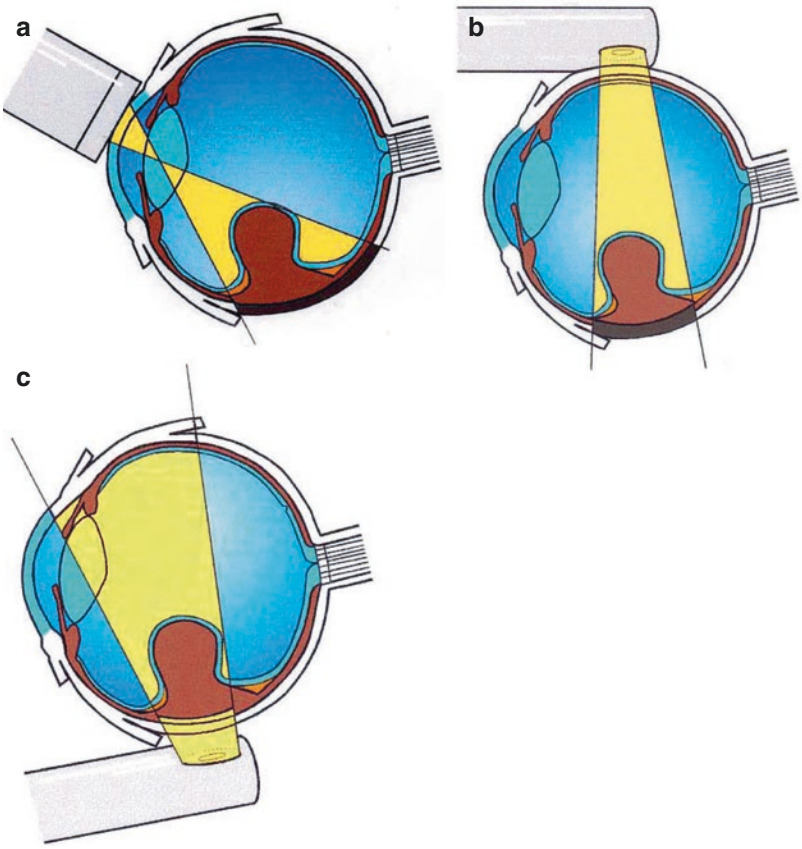

Fig. 1.4 Techniques of transillumination. Tumor extension assessed by trans-pupillary transillumination (**a**), trans-ocular transillumination (b), and trans-scleral transillumination (**c**). Note the exaggeration of posterior tumor extension with trans-pupillary transillumination [Reprinted from Damato [2]. With permission from Elsevier]

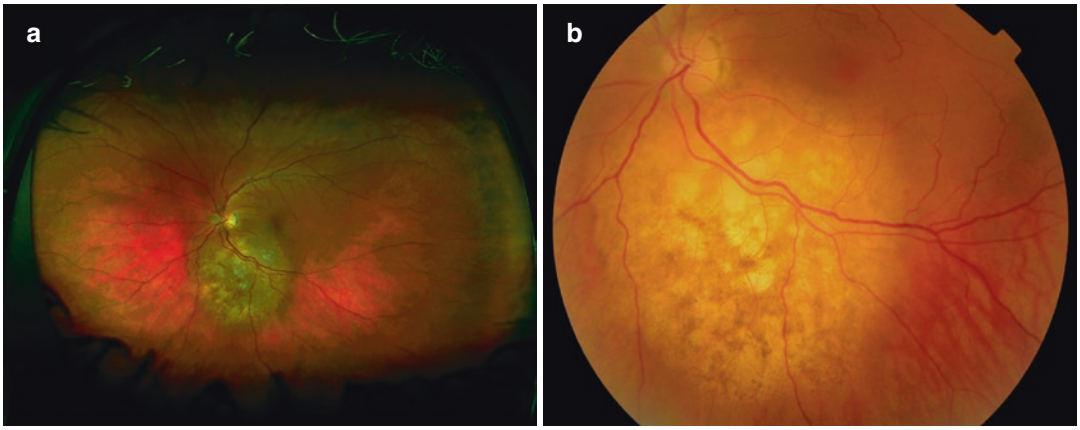

Fig. 1.5 Color photos of the metastasis from a lung adenocarcinoma in a 47-year-old woman. The tumor appears pigmented with the Optos camera (**a**) but not with the Topcon (**b**)

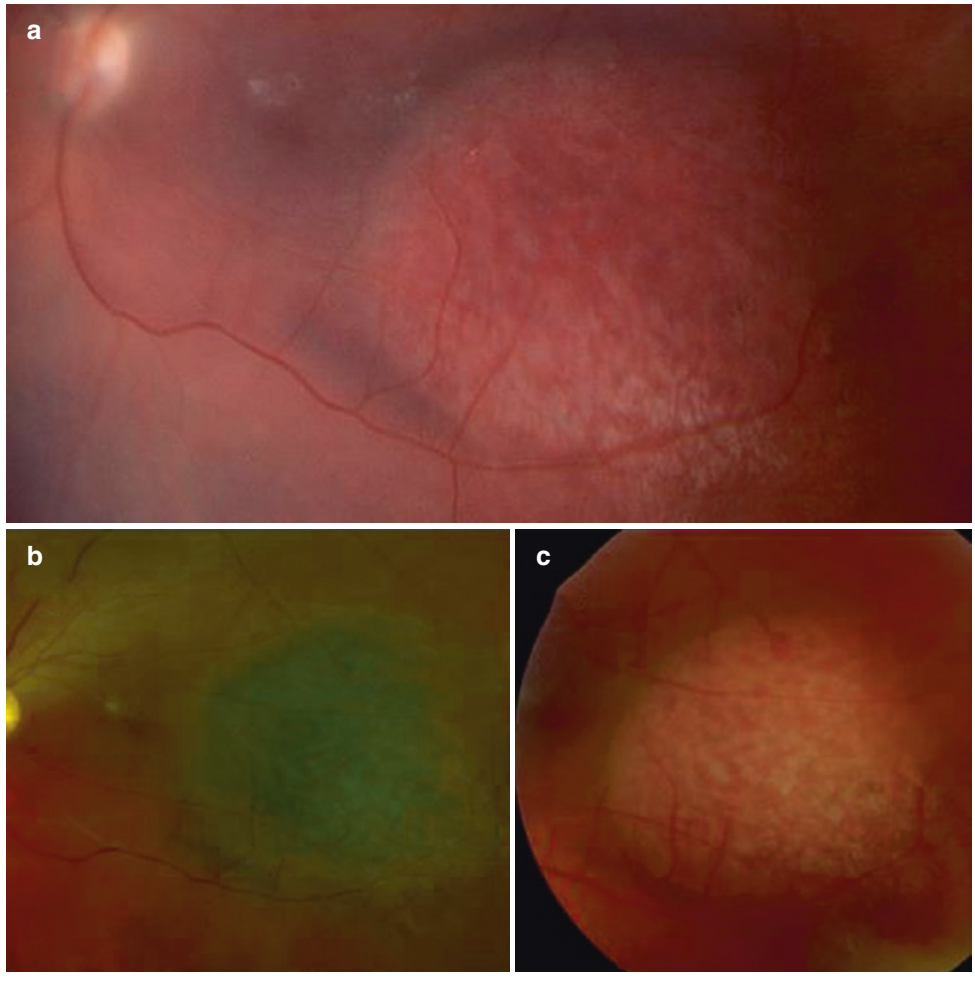

Fig. 1.6 Color photos of a choroidal hemangioma photographed with the Panoret (**a**), Optos (**b**), and Topcon (**c**)

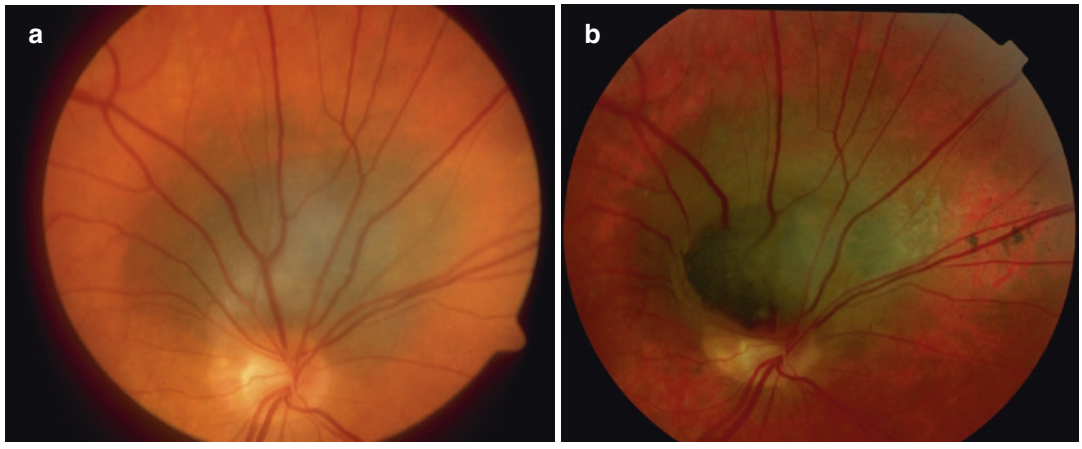

Fig. 1.7 Sequential color photographs of the right fundus of a 60-year-old man showing growth of a melanocytic tumor over a period of 13 years. Tumor appearances in 2000 (**a**) and in 2013 (**b**), with rupture of Bruch's membrane and development of a collar-stud shape, with minimal lateral extension

tent magnification or light exposure. Pseudogrowth can also occur because of retinal flattening, scleral flattening, and extension of secondary changes in the overlying retinal pigment epithelium [5].

Ancillary Tests

Ancillary investigations such as color photography, autofluorescence imaging, optical coherence tomography, angiography, and ultrasonography are discussed in detail elsewhere in this series [6].

Conclusion

The different examination techniques described in this chapter need to be used selectively. Each requires special expertise in performing the test and to ensure that the results are interpreted properly.

References

1. Bailey IL, Lovie JE. New design principles for visual acuity letter charts. Am J Optom Physiol Optic. 1976;53(11):740–5.
2. Damato B. Ocular tumours: diagnosis and treatment. Oxford: Butterworth-Heinemann; 2000.
3. Kernt M, Schaller UC, Stumpf C, et al. Choroidal pigmented lesions imaged by ultra-wide-field scanning laser ophthalmoscopy with two laser wavelengths (Optomap). Clin Ophthalmol. 2010;4:829–36.
4. Heimann H, Jmor F, Damato B. Imaging of retinal and choroidal vascular tumours. Eye (Lond). 2013;27(2):208–16.
5. Schalenbourg A, Zografos L. Pitfalls in colour photography of choroidal tumours. Eye (Lond). 2013;27(2):224–9.
6. Singh AD, Damato B, editors. Clinical ophthalmic oncology. Basic principles and diagnostic techniques. 3rd ed. Berlin/Heidelberg: Springer; 2019.

Classification of Uveal Tumors

2

Bertil E. Damato and Sarah E. Coupland

Introduction

Tumors of the same class should share a unique combination of features, which distinguishes them from all other classes [1, 2]. Classification, therefore, is the process of defining different tumor entities and correlating these with each other in a hierarchical manner based on the putative cell of origin. Classification also involves "grading" of tumor cell morphological features and consideration of their immunohistochemical and genetic profiles. It does not include tumor "staging," which determines the extent of tumor involvement and hence the type of treatment required (i.e., local versus systemic treatment).

Tumor classification has several uses. It can help the clinician to consider all relevant conditions when preparing a differential diagnosis. It can improve prognostication, by predicting how the tumor is likely to behave. This, in turn, can enhance treatment planning and enables proper evaluation of the results of treatment. Tumor classification also improves communication by allowing standardization of disease categorization in multicenter studies. Classification is also valuable in research, contributing to investigations in tumor biology (Box 2.1).

Box 2.1. Classification of Uveal Tumors

- Classification of tumors contributes to diagnosis, prognostication, treatment planning, evaluation of treatment results, communication between treatment centers, and oncological research.
- Tumors can be classified according to location, etiology, histopathology, histogenesis, and other methods.
- Each classification has its advantages and disadvantages in any particular situation so that different classification methods complement each other.
- Tumor classification must be distinguished from staging.

Classification of Uveal Tumors

Uveal tumors can be classified according to location, etiology, histopathology, histogenesis, genotype, and various other ontological methods. Each approach has its advantages and limitations.

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A classification based on tumor location within the uvea would need to mention some tumors more than once if these can arise at different sites, and, furthermore, it can be impossible to locate the origin of an extensive tumor. A classification that is superior in one situation may not be useful in other circumstances. For example, a histopathologic classification is helpful in a pathology laboratory but of limited value in an ophthalmic clinic when the patient is first seen, that is, before the tissue has been examined histologically.

This chapter considers some conditions that are not strictly uveal, because these might be mistaken for a uveal tumor. For example, adenomas, adenocarcinomas, congenital hypertrophy of the retinal pigment epithelium, and iris cysts are all epithelial but need to be included in the differential diagnosis of several uveal tumors. For the same reasons, conditions, such as varix of the vortex vein ampulla, are mentioned, even if they are not neoplasms at all.

Strictly speaking, the lists provided are not classifications, because they include tumors that are not biologically, clinically, and histologically related. In any case, it is hoped that this review will make it easier for clinicians to recall all relevant conditions in the differential diagnosis when the need arises, a mental feat that is facilitated by categorizing the different tumors and "pseudotumors" into meaningful groups.

Etiologic Classification

This system categorizes uveal tumors according to their underlying causes, that is, as congenital, traumatic, inflammatory, neoplastic, degenerative, and idiopathic (Table 2.1). This is by no means an exhaustive list. First, the anatomical listing is only approximate, because tumors can arise in atypical locations. Second, the etiology of some tumors is not known (e.g., choroidal osteomas) (Fig. 2.1). It is important to appreciate that terminology may also influence clinical management inappropriately. For example, the term "suspicious nevus" may encourage passive clinical management, whereas if the same lesion is called "suspicious melanoma," it is perhaps more likely to be treated. It may therefore be preferable to refer to an equivocal melanocytic tumor as an "indeterminate melanocytic tumor" or "melanocytic tumor of unknown malignancy." Whether such a tumor is nevus, melanoma, or indeterminate is, of course, subjective if diagnosis is based on ophthalmoscopy alone. Finally, some tumors such as neurilemmoma, neurofibroma, and leiomyoma are classified separately despite being clinically indistinguishable.

Histopathologic Classification

Histopathologic classification categorizes uveal neoplasms according to their cellular morphology, immunohistochemical, and genetic profiles. The World Health Organization (WHO) Classification of Tumours of the Eye has classified uveal tumors according to (a) anatomical site, (b) histologic type, and (c) genetic profiles [3]. This classification was developed by pathologists and ophthalmologists, specifically for diagnosing tumors based on histopathologic material. It provides differential diagnoses for each entity, including those that are nonneoplastic, such as inflammation or degenerative conditions. A summary of the WHO uveal tumor classification according to cell of origin is provided in Table 2.2.

Histogenetic Classification

Histogenetic classification groups tumors hierarchically according to their embryonic lineage, with tumors being subclassified according to whether they originate from ectodermal, endodermal, or mesodermal cells [2]. Tumors are further subclassified according to whether they arise from primitive cells (e.g., totipotential cells forming teratomas) or differentiated cells (e.g., melanocytes). Proponents of this biological system of classification argue that it is simple, comprehensive, and capable of developing as molecular biology improves knowledge about different tumor types. Another advantage of this classification is that tumors with the same lineage

Table 2.1 Uveal tumors classified according to pathogenesis and location

Category		Subtype	Location		
			Iris	Ciliary body	Choroid
Congenital	Hamartoma	Lisch nodules	Y		
	Choristoma	Lacrimal gland choristoma	Y	Y	
		Osseous choristoma			Y
		Stromal iris cyst	Y		
Inflammatory	Infectious	Granuloma (e.g., Tuberculosis)	Y	Y	Y
	Noninfectious	Sarcoidosis	Y	Y	Y
		Juvenile xanthogranuloma	Y		
		Scleritis		Y	Y
		Uveal effusion		Y	Y
Neoplastic/ Hyperplastic	Melanocytes	Melanocytic nevus	Y	Y	Y
		Melanocytosis	Y	Y	Y
		Melanocytoma	Y	Y	Y
		Bilat. diffuse uveal melanocytic hyperplasia		Y	Y
	Blood vessels	Circumscribed hemangioma			Y
		Diffuse hemangioma		Y	Y
		Hemangiopericytoma	Y		
		Racemose angioma	Y		
	Fibroblasts	Neurofibroma		Y	Y
	Neural tissue	Neurilemmoma		Y	Y
	Muscle	Leiomyoma	Y	Y	Y
		Mesectodermal leiomyoma	Y	Y	
	Lymphocytes	Reactive lymphoid hyperplasia or chronic inflammation	Y	Y	Y
		Melanoma	Y	Y	Y
	Muscle	Rhabdomyosarcoma	Y	Y	
	Secondary	Melanoma/carcinoma	Y	Y	Y
	Hemopoietic	Lymphoma	Y	Y	Y
		Leukemia	Y	Y	Y
	Metastatic	Carcinoma/sarcoma	Y	Y	Y
Traumatic		Foreign body	Y	Y	Y
		Suprachoroidal hematoma			Y
Degenerative		Disciform lesion (from choroidal neovascularization)			Y
		Sclerochoroidal calcification			Y
Idiopathic		Varicose vortex vein			Y

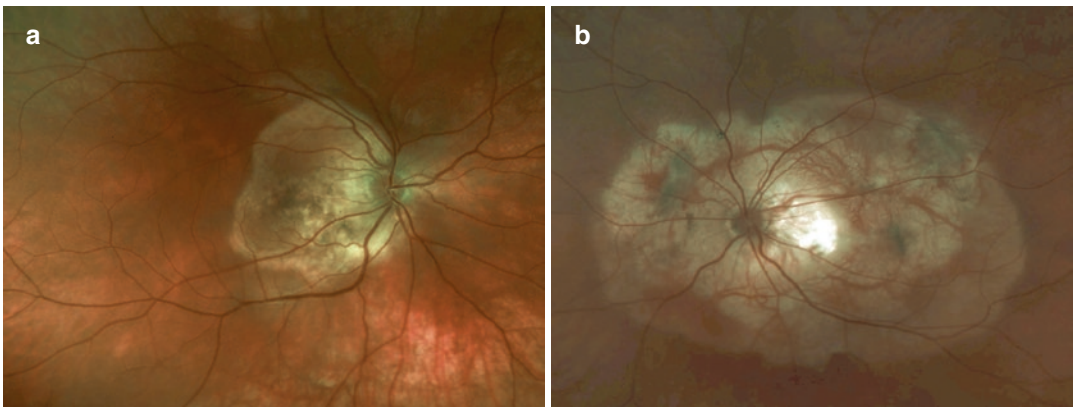

Fig. 2.1 Choroidal osteomas in the right eye (**a**) and left eye (**b**) of a 15-year-old woman. The etiology is not known as these tumors can be bilateral and have been reported in siblings