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Imaging of retinal and choroidal vascular tumours

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Abstract

The most common intraocular vascular tumours are choroidal haemangiomas, vasoproliferative tumours, and retinal haemangioblastomas. Rarer conditions include cavernous retinal angioma and arteriovenous malformations. Options for ablating the tumour include photodynamic therapy, argon laser photocoagulation, trans-scleral diathermy, cryotherapy, anti-angiogenic agents, plaque radiotherapy, and proton beam radiotherapy. Secondary effects are common and include retinal exudates, macular oedema, epiretinal membranes, retinal fibrosis, as well as serous and tractional retinal detachment, which are treated using standard methods (ie, intravitreal anti-angiogenic agents or steroids as well as vitreoretinal procedures, such as epiretinal membrane peeling and release of retinal traction). The detection, diagnosis, and monitoring of vascular tumours and their complications have improved considerably thanks to advances in imaging. These include spectral domain and enhanced depth imaging optical coherence tomography (SD-OCT and EDI-OCT, respectively), wide-angle photography and angiography as well as wide-angle fundus autofluorescence. Such novel imaging has provided new diagnostic clues and has profoundly influenced therapeutic strategies so that vascular tumours and secondary effects are now treated concurrently instead of sequentially, enhancing any opportunities for conserving vision and the eye. In this review, we describe how SD-OCT, EDI-OCT, autofluorescence, wide-angle photography and wide-angle angiography have facilitated the evaluation of eyes with the more common vascular tumours, that is, choroidal haemangioma, retinal vasoproliferative tumours, and retinal haemangioblastoma.

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Introduction

Intraocular vascular tumours comprise choroidal haemangiomas, retinal haemangioblastomas, vasoproliferative tumours, and very rare lesions, such as cavernous retinal angiomas and arterio-venous malformations.

The treatment of retinal and choroidal vascular tumours has progressed considerably in recent years.^{1,2} In addition to conventional radiotherapy, cryotherapy, and laser photocoagulation, new therapeutical options include anti-VEGF pharmacotherapy, proton beam radiotherapy, photodynamic therapy, and small gauge vitrectomy.^{3–8} These have been reviewed elsewhere and are therefore not discussed in the present article.

These therapeutic advances are, in part, due to the tremendous advances in ophthalmic imaging that are now routine. Spectral domain optical coherence tomography (SD-OCT), enhanced depth imaging optical coherence tomography (EDI-OCT), wide-angle photography/angiography/autofluorescence imaging all provide qualitative and quantitative information that previously was unavailable.^{9–13} These methods have become indispensable in the management of patients with a vascular tumour.² Because of their novelty, there is scope for an up-to-date discussion of their relevance to vascular tumours of the eye.

In this article, we review the role of novel imaging techniques in the management of the more common vascular tumours of the

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eye, that is, choroidal haemangiomas, vasoproliferative tumours, and retinal haemangioblastomas.

Recent developments in imaging of the ocular fundus

Wide-angle photography and angiography

With wide-angle photography systems, multiple or extensive areas of interest can be visualized on one photograph. Sequential images can now be reviewed in high resolution side by side on a computer screen, making it easier to detect change.

RetCam (Clarity Medical Systems, Inc., Pleasanton, CA, USA) combines a fiberoptic digital photography system. RetCam is mainly restricted to paediatric ophthalmology.¹⁴

The Panoret-1000 (Medibell Medical Vision Technologies, Ltd., Haifa, Israel) combines a contact wide-angle camera with a fiberoptic light source that is placed on the sclera.^{9,15} It produces excellent pictures with high resolution and natural colours, and has successfully been deployed in ocular oncology centres.^{9,15} At the time of writing this article, the Panoret-1000 is no longer commercially available.

Optomap ultra-widefield imaging (Optos PLC, Dunfermline, UK) is a non-contact system incorporating a scanning laser ophthalmoscope with two wavelengths (532 and 633 nm). The main advantages are the high resolution, the extensive focal depth, the ease with which sequential images are compared, the image quality in patients with media opacities, and its tolerance by photophobic patients.¹⁶ It identifies macular pathology as effectively as conventional high-resolution digital imaging.¹⁶ One disadvantage is that some areas of the retinal periphery can be obscured by eyelashes, vitreous opacities, or the edge of an intraocular lens.¹⁶ Furthermore, the system generates dual colour images (red and green) so that the apparent colour of some vascular tumours can be very different from the true clinical appearance.

RetCam, Optomap, and cSLO angiography systems all enable wide-angle fluorescein angiography. With wide-angle contact lenses, ICG angiography is also possible.

SD-OCT

Standard OCT has been in clinical use since 1995.¹⁷ The introduction of the high-resolution SD-OCT represents a major advance.^{13,17,18} More scans with an axial resolution up to 5 μ m are obtained more rapidly, also covering a larger area of the fundus.^{13,18} Individual retinal layers up to the junction of the photoreceptor

inner and outer segments can now be visualized.¹³ With vascular tumours, SD-OCT scans are mainly used for the detection and quantification of macular changes.¹⁷ Another important application is the detection of retinal changes associated with vascular tumours, for example, epiretinal membranes or retinal atrophy in areas overlying a vascular tumour. SD-OCT has only a minor role in the differential diagnosis of vascular tumours, as this technique is useful only for the examination of posterior lesions and images only the superficial 1 mm of the retina and choroid.^{18,19}

Modern SD-OCT scanners also enable 3D reconstruction of retinal and superficial choroidal tumours.^{17,20} With new montage techniques, an area of 50° × 35° can be analysed.²¹

EDI-OCT

With standard OCT, the choroid and sclera show a relatively low resolution due to the light scattering from the retinal pigment epithelium (RPE) and choriocapillaris.¹⁸ By pushing the OCT objective lens closer to the eye, an inverted image with higher resolution of the choroid can be obtained.²² This 'enhanced depth imaging' may be useful in measuring and characterizing lesions <1 mm thick that are too thin to be measured with conventional ultrasonography.¹⁹

Fundus autofluorescence

Autofluorescence detects the natural emission of light by intraocular structures after excitation by light of a different wavelength. This investigation amplifies and averages multiple sequential images, obtained with modern cSLO machines.¹² Two different methods of autofluorescence imaging exist:²³

Fundus autofluorescence is recorded with the 488 nm excitation and >500 nm emission wavelength settings. The main fluorophore is lipofuscin, which is the end-product of phagocytosed photoreceptor outer segments, mostly accumulating within RPE cells. Increased autofluorescence indicates greater metabolic activity of the RPE cells, which occurs before cell death.¹² An important benefit of autofluorescence lies in detection of disturbances of the RPE–photoreceptor complex, which cannot be identified with other imaging methods.^{10,12} Decreased or absent fluorescence is a sign of dead or permanently damaged RPE cells.¹²

Near-infrared autofluorescence is recorded with the 787 nm and >800 nm settings of indocyanine green angiography. The main fluorophore detected is melanin, which is localized in the apical part of RPE cells. Disturbances in the near-infrared autofluorescence can

indicate injuries in the RPE cell layer and photoreceptor complex.

Wide-angle autofluorescence is now available using the Optomap system.²⁴ Initial results suggest that wide-angle autofluorescence may be more sensitive in identifying peripheral fundus changes than pseudo-colour imaging due to the higher contrast of the images.¹⁰

Imaging of vascular tumours

Choroidal haemangioma

Most circumscribed choroidal haemangiomas can readily be diagnosed with indirect ophthalmoscopy and ultrasonography.^{1,25} They appear as indistinct, non-pigmented, orange-to-red lesions at the posterior pole and near the optic disc. Associated clinical features are exudative retinal detachment, macular oedema, pigmentary changes within the RPE, subretinal fibrosis over the surface of the lesion, and orange pigment.

Circumscribed haemangiomas are often misdiagnosed as choroidal melanoma or metastasis on referral to tertiary centres.²⁵

The apparent colour of choroidal haemangiomas varies according to the imaging method used. With scanning laser systems, choroidal haemangiomas may appear brown so that they are more likely to be mistaken for choroidal melanoma (Figure 1). This is of practical importance when evaluating fundus pictures via e-mail. By contrast, the Panoret-1000 system depicts choroidal haemangioma with their true, red colour (Figure 1).

On ultrasonography, choroidal haemangiomas have a high internal acoustic reflectivity matching the reflectivity of the surrounding choroid. This helps to differentiate choroidal haemangiomas from other choroidal tumours, such as melanoma.²⁵ Ultrasonography is also used to measure tumour dimensions. Fluorescein angiography adds little diagnostic information.²⁶ In typical cases, it demonstrates an early filling of the tumour vessels and choroidal vasculature before filling of the retinal vessels (Figure 2).

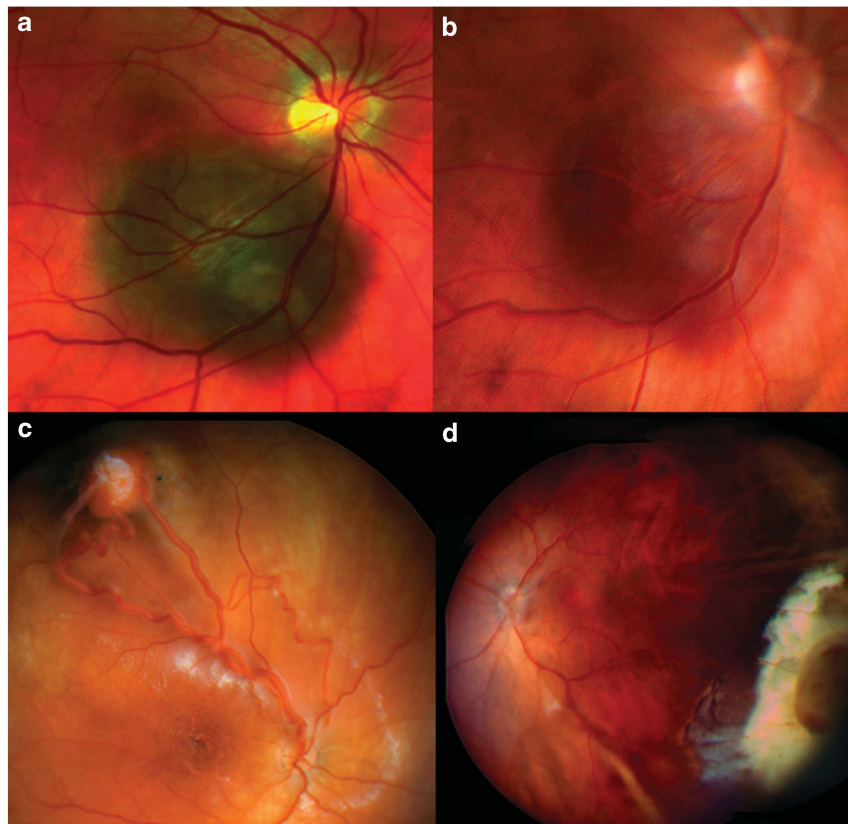


Figure 1 Colour and wide-angle imaging of vascular tumours. (a) Circumscribed haemangioma recorded with the Optomap system. The tumour appears darker and browner and mimics a choroidal melanoma. (b) Same tumour as in (a) imaged with the Panoret camera. A vivid reddish colour of the haemangioma is noted. (c) Peripheral retinal haemangioblastoma imaged with the Panoret camera. The peripheral angioma, dilated feeder vessels, the posterior pole with macular oedema, the optic disc, and the preretinal fibrosis over the tumour can all be documented in one photograph. (d) Vasoproliferative retinal tumour in the temporal periphery imaged with the Panoret system. Typical associated exudative retinal changes and pigmentary changes of the RPE.

The intrinsic vasculature of haemangiomas displays hyperfluorescence through all phases of the angiography.²⁵ ICG angiography and wide-angle ICG angiography are thought to be more useful diagnostically than fluorescein angiography.²⁶ The typical ICG angiographic features of choroidal haemangioma are the appearance of strongly hyperfluorescent intratumoural vessels in the arterial phase, followed by a significant wash-out with hypofluorescence of the tumour relative to the surrounding chorioid in the late phases (30–60 min).²⁶ Fluorescein and ICG angiography have traditionally been used to monitor the vascular activity of choroidal haemangiomas following treatment. This has now been superseded by monitoring the secondary effects with SD-OCT.⁸

The value of SD-OCT in the assessment of choroidal haemangioma lies in the detection and quantification of associated retinal changes (Figure 3). These include sub- and intraretinal fluid, retinal schisis, photoreceptor loss, and retinal atrophy.^{17,20,27,28} However, the retina overlying the haemangioma may be normal.²⁰ The RPE layer usually shows a dome-shaped uninterrupted elevation over the haemangioma.^{20,28} Disturbances in the

RPE layer corresponding to subretinal fibrosis can also be seen in chronic cases. The macular changes detectable with SD-OCT are foveal cystoid oedema and/or subfoveal fluid. SD-OCT, therefore, is useful for monitoring treatment response, for example, regression of macular oedema or exudative retinal detachment.²⁹ Recurrent subretinal fluid following therapy can be detected before the vision deteriorates and before this fluid becomes apparent clinically.^{29,30} At baseline, SD-OCT images can also be used to distinguish acute (exudative detachment with preserved retinal architecture) from chronic changes (retinal atrophy). Together with the evaluation of the inner segment/ outer segment photoreceptor line and the integrity of the RPE layer, this information may be useful when considering treatment options and potential outcome (Figure 3). Preservation of outer retinal thickness and integrity of the inner segment/outer segment photoreceptor line are important prognostic factors for visual recovery following treatment.²⁸

Regarding SD-OCT imaging of the haemangioma itself, the anterior surface of the tumour appears hyporeflective.²⁰ This is not detectable using standard

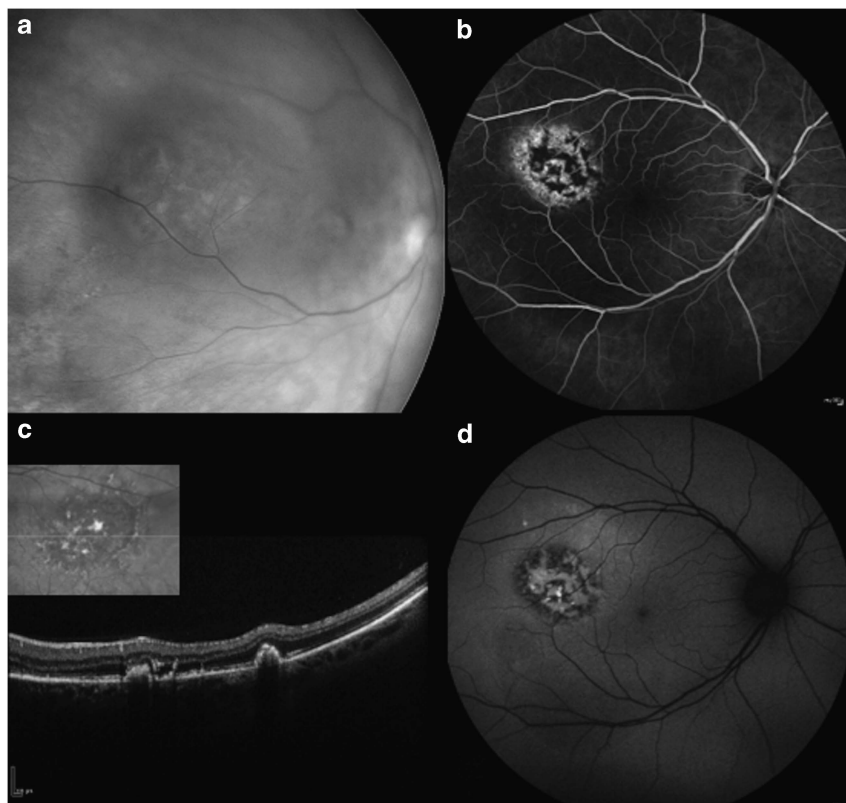


Figure 2 Multimodal imaging of circumscribed choroidal haemangioma. (a) Panoret wide-angle fundus photograph demonstrating the circumscribed choroidal haemangioma. (b) Wide-angle 50° fluorescein angiography demonstrating hyperfluorescence of the haemangioma in the arterio-venous phase. (c) SD-OCT with fibrotic changes in the RPE layer. The tumour is not visualized with standard SD-OCT settings. (d) Fundus autofluorescence showing hyperfluorescence of the clinically visible orange pigment over the haemangioma.

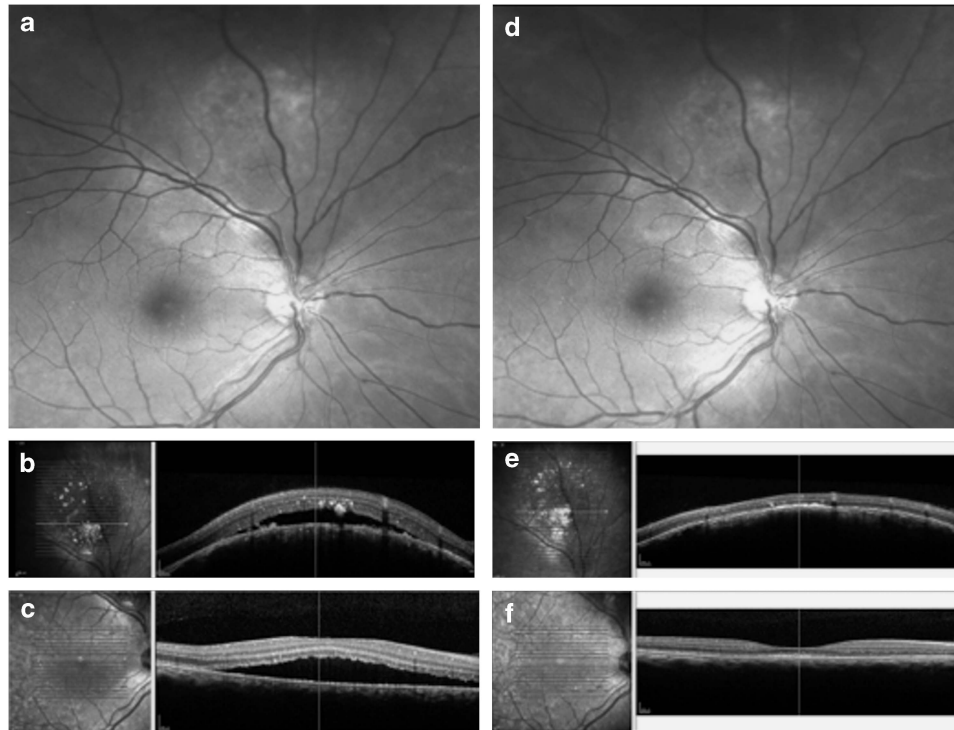


Figure 3 SD-OCT in the management of circumscribed choroidal haemangioma. (a) Pre-treatment Optomap picture of a circumscribed choroidal haemangioma above the disc. (b) SD-OCT over the haemangioma, demonstrating fluid between the photoreceptor and the RPE layer. The RPE layer is interrupted. No details of the haemangioma can be visualized. (c) SD-OCT over the fovea. The exudative detachment extends into the fovea. (d) Same patient 8 months following PDT using standard parameters. On the Optomap picture, no significant differences can be seen. (e) SD-OCT over the tumour following PDT. Regression of subretinal fluid and thinning of the retinal layers over the haemangioma. (f) SD-OCT over the fovea following PDT. Complete regression of the subretinal fluid. No indication for additional treatment.

SD-OCT scans.²⁸ Interestingly, details of the superficial choroidal structures reappear under the RPE band following successful treatment of the choroidal haemangioma.²⁸ On EDI scans, circumscribed choroidal haemangiomas appear as a low-to-medium reflective band with a homogenous signal and intrinsic spaces.¹⁹ They can be distinguished from normal surrounding choroidal tissue, but their posterior border is detectable only in tumours with a thickness of <0.9 mm.¹⁹

Autofluorescence imaging shows choroidal haemangioma to be hypo- or isofluorescent relative to the surrounding tissue.²⁷ The autofluorescence shows mainly a granular pattern. Orange pigment overlying the haemangioma is strongly hyperfluorescent, whereas localized fibrosis and RPE atrophy are hypofluorescent (Figure 2). Fresh subretinal fluid is hyperfluorescent. By contrast, chronic subretinal fluid is hypofluorescent relative to the surrounding tissue.²⁷ Following treatment, the relative hypofluorescence of the haemangiomas is more pronounced.²⁷

Diffuse choroidal haemangiomas are usually associated with Sturge–Weber syndrome. They more closely resemble a diffuse choroidal angiomas than a

localized vascular tumour.⁸ On ultrasonography, the extension of the lesion usually exceeds the apparent diameter based on indirect ophthalmoscopy. Wide-angle ICG angiography is useful in determining the extent of the haemangioma. With SD-OCT, associated retinal changes resemble those of occurring in circumscribed haemangioma.³¹ Similarly, the autofluorescence pattern of diffuse choroidal haemangioma is similar to that of circumscribed lesions.²⁷

Retinal vasoproliferative tumour

Retinal vasoproliferative tumours comprise a spectrum of focal-to-diffuse vascularized retinal lesions having a prominent glial component (Figure 1).^{1,32} These usually appear as pink, retinal tumours or diffuse fibrotic thickening, usually in the inferior fundus periphery, often with a haemorrhagic component. Associated changes are exudative retinal detachment, macular oedema, sub-, intra-, and epiretinal fibrosis, hyper- and hypo-pigmentation of the RPE, and cellular infiltrates in the vitreous. Macular changes exist in 59% of idiopathic vasoproliferative tumours of the retina and in 92% of

cases that are associated with other ophthalmological diseases.³³

Because of their pre-equatorial location, many retinal vasoproliferative tumours cannot be photographed with conventional imaging methods, and some are also beyond the reach of wide-angle cameras. Nevertheless, wide-angle photography is useful for monitoring of associated retinal changes. Some vasoproliferative retinal tumours are initially managed by observation, and in such cases, wide-angle photography aids evaluation of the lesions so as to determine the need for treatment. Fluorescein angiography can be helpful in the initial diagnosis of vasoproliferative retinal tumours. For example, it helps to differentiate these from peripheral exudative haemorrhagic chorioretinopathy.³⁴ In contrast to retinal capillary haemangioblastoma, retinal feeder vessels are only mildly dilated on fluorescein angiography. Wide-angle angiography is particularly useful in demonstrating the vasoproliferative nature and vascular supply of these lesions. Because of the retinal localization of these lesions, ICG angiography does not add useful information.

Most vasoproliferative tumours of the retina are too peripheral to be imaged with standard SD-OCT. Posterior lesions demonstrate retinal inner layer disorganization and posterior shadowing.³⁵ SD-OCT is a useful imaging tool in the management of such lesions.^{17,33} In a large number of cases, the long-term visual disability that is caused by retinal vasoproliferative tumours will be related to retinal changes in the macular region and not by the tumour itself. In particular, there is a high incidence of epiretinal membrane formation and macular oedema. Our current treatment strategy is based on SD-OCT imaging and involves small-gauge vitrectomy with peeling of epiretinal membranes and/or anti-VEGF or steroid injections for macular oedema. This is in addition to treatment of the peripheral vasoproliferative tumour by laser photocoagulation, photodynamic therapy, or brachytherapy.

After initial treatment, SD-OCT is used to monitor treatment response and indicate the need for additional therapy. Following successful ablation of the vasoproliferative tumour, regression of the associated retinal exudative changes occurs. SD-OCT and wide-angle autofluorescence imaging demonstrate the extent of any permanent damage in the photoreceptor–RPE complex. Typical findings with SD-OCT are retinal and RPE atrophy. With autofluorescence, hyperfluorescence of areas bordering the exudative changes as well as a relative hypofluorescence in the area affected by the exudative detachment can be seen. Following treatment and regression, the areas of significant retinal damage and atrophy appear hypofluorescent.

Retinal haemangioblastoma

Retinal haemangioblastomas can affect any part of the fundus and vary greatly in their clinical appearance.^{36,37} They may occur sporadically or with the von Hippel–Lindau syndrome (Figure 1).^{38,39} Small tumours appear as tiny, red dots or as retinal teleangiectasia. On ophthalmoscopy, the angiomatous nature may sometimes be obscured by epiretinal fibrosis so that the only visible clues may be the associated changes in the surrounding retinal vessels. Larger angiomas can appear as a pink-orange mass of coiled vascular structures rather than a large, blood-filled angioma. Dilated feeder vessels and an epiretinal fibrotic reaction are typical of larger haemangioblastomas (Figure 1). Visual loss is caused by intra- and subretinal exudates, macular oedema, exudative retinal detachment, epiretinal membrane formation, and tractional retinal detachment. It is important to identify retinal haemangioblastomas and their associated complications at an early stage as advanced lesions are not usually controlled with conventional laser- or cryotherapy alone.⁷ These large lesions are usually accompanied by severe exudative and vitreoretinal traction. Such advanced disease often results in a blind and painful eye, necessitating enucleation in about 10% of patients.³⁶

Juxtapapillary retinal haemangioblastomas differ clinically from peripheral lesions.³⁹ They are classified as endophytic (ie, intravitreal), exophytic (ie, subretinal), or sessile (ie, intraetinal). Small angiomas on the disc initially resemble splinter haemorrhages. When they enlarge, they become visible more as a diffuse thickening of the retina. Only in the advanced stages do they develop a typical angiomatous appearance. These tumours are associated with exudative and glial retinal changes as outlined above. In contrast to peripheral haemangioblastomas, dilated feeder vessels do not develop.

Wide-angle photography is extremely useful in the management of patients with retinal haemangioblastoma, particularly in the presence of the von Hippel–Lindau syndrome (Figures 1 and 4). This is because such patients with VHL can have multiple tumours, with new lesions developing over time. In addition, they often develop a variety of sight-threatening complications that need to be detected and monitored. These include exudation, macular oedema, exudative and tractional retinal detachment, and epiretinal membrane formation (Figures 1 and 4). The panoramic photographic documentation now enables the treating ophthalmologist to analyse changes over time with greater ease and accuracy than was hitherto possible.

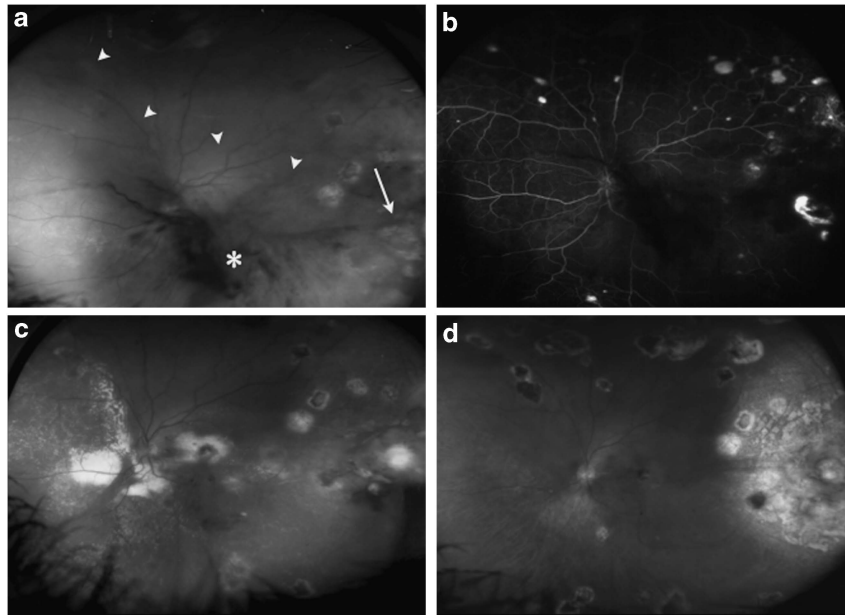


Figure 4 Patient with multiple retinal haemangioblastoma associated with von Hippel–Lindau syndrome in the left eye. The patient was referred following unsuccessful laser and cryotherapy. (a) At the initial examination in our institution, there was a large and active haemangioblastoma in the temporal periphery (arrow) associated with a vitreous haemorrhage (*) and a near-total exudative retinal detachment (arrowheads). (b) The wide-angle fluorescein angiography highlights more than 20 active haemangioblastoma (visible as leaking spots during the angiography). (c) Same patient 4 months after initial treatment with brachytherapy and laser. Regression of the large angioma in the temporal periphery. Collection of lipid exudates in the area of the previous exudative retinal detachment. (d) Same patient 17 months following brachytherapy and multiple sessions of laser photocoagulation. Complete regression of all previously active haemangioblastoma. Regression of the exudative retinal detachment and lipid exudates.

Fluorescein angiography is still valuable in assessing patients with retinal haemangioblastomas. In addition to feeder vessels, these tumours show early hyperfluorescence during the arterial phase with increasing but variable leakage during the later phases of the angiogram.³⁵ Wide-angle angiography greatly facilitates the detection of small angiomas and is more sensitive than indirect ophthalmoscopy and fundus photography (Figure 4).³⁷ ICG angiography can be useful in selected cases, particularly with juxtapapillary haemangioblastomas, demonstrating vasculature that would otherwise be obscured by early fluorescein leakage.

The value of SD-OCT in the management of patients with retinal haemangioblastoma lies in the identification and monitoring of associated retinal changes.⁴⁰ These include macular oedema, retinal atrophy, retinal detachment and epi- or subretinal membrane formation, which are not as well demonstrated by indirect ophthalmoscopy and other imaging methods. Early identification and treatment of these effects may have a greater influence on visual outcome than treatment of the tumour itself. When located near the posterior pole, the haemangioblastoma can be visualized on the SD-OCT scan (Figure 5). It appears as an optically-dense, inner-retinal mass with

posterior shadowing or thickening and disorganization of the retinal layers.^{17,40,41}

Fundus autofluorescence can provide additional information regarding the activity state and viability of the photoreceptor–RPE complex. Areas near exudative retinal changes usually show hyperfluorescence, whereas atrophic or permanently damaged retina appears hypofluorescent.

Summary and conclusion

The past decade has seen much progress in the management of patients with a vascular tumour of the eye. This advance is closely linked to the development of new imaging methods, in particular, SD-OCT and wide-angle photography. When patients are initially managed by observation, SD-OCT and autofluorescence imaging indicate the chances of functional improvement with treatment. Furthermore, early detection of subclinical macular oedema or epiretinal membranes can allow treatment before visual loss occurs, enhancing long-term outcomes.

Thanks to improved imaging, current treatment strategies for vascular tumours have fundamentally changed. Previously, only the tumour was treated, with secondary effects being managed at a later stage; today,

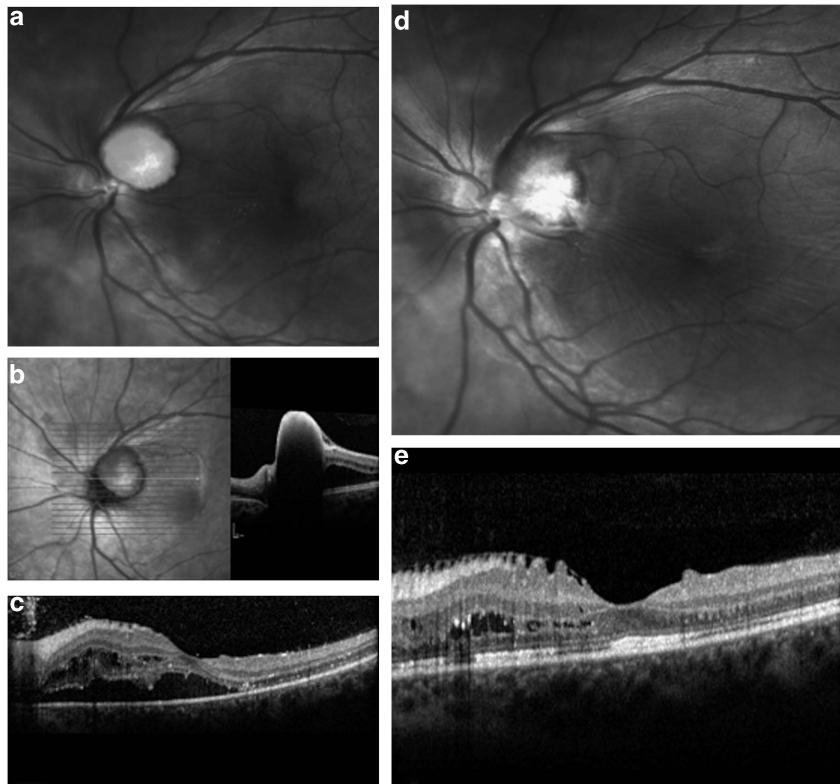


Figure 5 Retinal haemangioblastoma on the disc not associated with von Hippel–Lindau syndrome. (a) Baseline fundus picture showing an endophytic peripapillary angioma with retinal exudates. (b) SD-OCT over the angioma. No retinal structures can be identified over the tumour. The angioma appears as an optically dense inner retinal mass with posterior shadowing. (c) SD-OCT over the macula. Intraretinal exudative changes and exudative retinal detachment involving the fovea. Visual acuity 6/18. (d, e) One year after PDT. (d) Fundus picture demonstrating a fibrotic reaction in the angioma following PDT. Visual acuity 6/9. (e) SD-OCT over the macula. Regression of intraretinal fluid and subretinal fluid following treatment.

both the primary tumour and the secondary effects are treated simultaneously from the outset.

Panoramic fundus photography has become indispensable, with a single image demonstrating not only the activity of the vascular lesion but also the associated exudative retinal changes, epiretinal membranes, areas of retinal traction, and any new lesions. Moreover, sequential high-resolution images greatly facilitate the assessment of disease activity and response to treatment.

New imaging methods are being deployed in routine clinical practice, and these include fundus autofluorescence, wide-angle autofluorescence, near-infrared autofluorescence, and EDI-OCT. It is likely that these new methods will further improve our understanding of vascular tumours of the retina and choroid and their secondary effects on the eye thereby enhancing the targeted treatment of these rare tumours.

Conflict of interest

The authors declare no conflict of interest.

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