

Pearls for Imaging and Diagnosis in Ocular Oncology

The use of new imaging modalities can help clinicians better understand the pathophysiology of intraocular tumors.

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The ability to examine and image the interior of the eye provides a powerful tool in the evaluation and management of intraocular tumors. Current and emerging instrumentation can acquire, edit, archive, retrieve, compare, make precise measurements, and transmit high quality digital images for diverse purposes, including patient care, treatment planning, teaching, and research.

Ocular imaging plays a key role in evaluating tumor location, thickness, basal dimensions, vascularity, architecture, tissue composition, and invasiveness. Imaging techniques help confirm the presence of and quantitate the amount of subretinal fluid, orange lipofuscin pigmentation, and other tumor-associated sequelae, and they facilitate the staging and classification of intraocular tumors. Imaging is important for following the response to therapy and evaluating treatment-related complications such as radiation retinopathy. Additionally, advances in imaging enhance our understanding of the pathophysiology of intraocular tumors.

FUNDUS PHOTOGRAPHY

Fundus photography remains a cornerstone in the management of intraocular tumors. It is used for documenting initial tumor characteristics such as pigmentation, basal dimensions, proximity to ocular structures, retinal detachment, and other associated features. Serial photography over time is also crucial for detecting growth in tumors that are observed and in documenting

response to therapy in those that are treated.

More recent improvements in technology include wider angle and nonmydriatic cameras and software that allows digital images to be adjusted for illumination, contrast, and other enhancements and to be assembled into montage images that simulate panoramic fundus photographs (Figure 1A).

Most software programs now contain measuring tools that allow precise calculation of tumor basal dimensions and distance to surrounding ocular structures. The Retcam (Clarity Medical, Pleasanton, CA) and similar hand-held devices allow digital fundus photography in the operating room, where it is used primarily for pediatric patients who require examination under anesthesia (Figure 1B).

ULTRASONOGRAPHY

Ophthalmic ultrasonography remains one of the most important diagnostic tools in the evaluation of intraocular tumors. Ultrasonography is particularly crucial in the presence of opaque media caused by cataract, vitreous hemorrhage, or other abnormalities that preclude direct visualization of the tumor using ophthalmoscopic techniques.

Standardized A-scan ultrasonography, performed with a machine that has been calibrated to tissue sensitivity, demonstrates tumor thickness, internal reflectivity, and spontaneous vascular pulsations. Uveal melanomas usually demonstrate low-to-medium internal reflectivity,

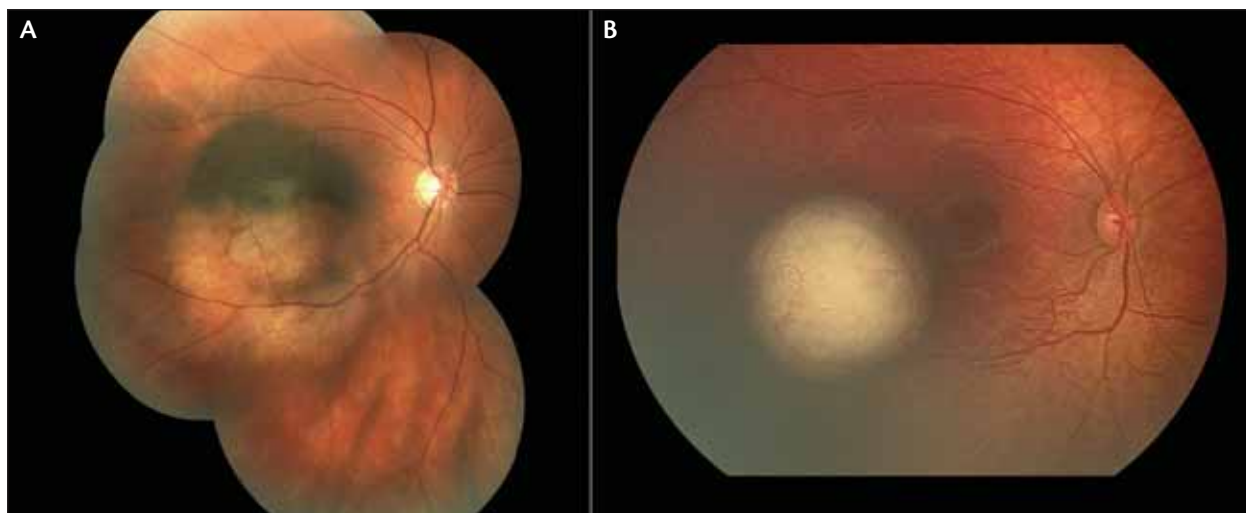


Figure 1. Fundus Photography. (A) Montage fundus photograph of a choroidal melanocytic tumor in which multiple color photos were digitally “pasted” together by computer software. (B) Fundus photograph of a child using the Retcam wide-field handheld digital imaging system showing a retinal mass with prominent vasculature consistent with retinoblastoma.

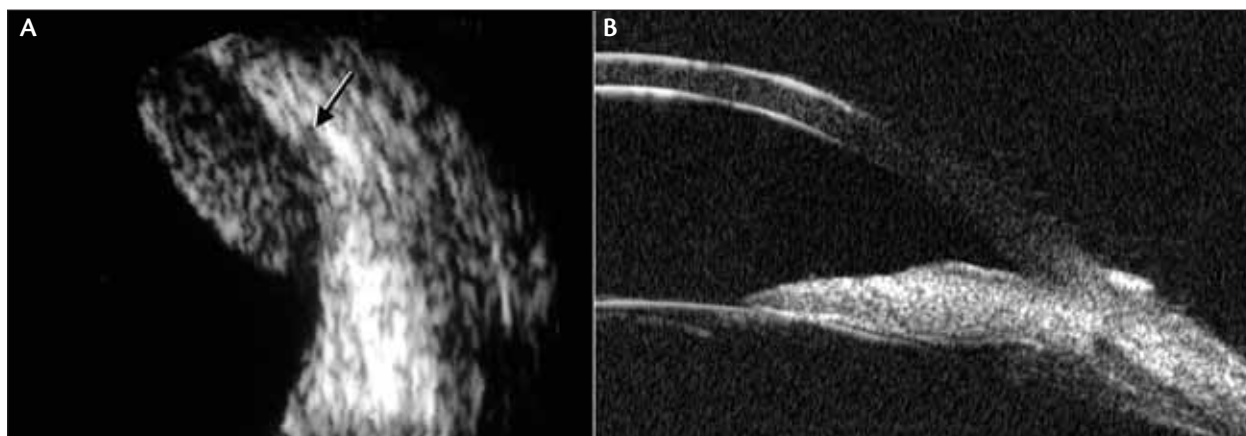


Figure 2. Ultrasonography. (A) B-scan ultrasound imaging showing a sonolucent choroidal mass associated with scleral invasion (arrow), consistent with uveal melanoma. (B) Ultrasound biomicroscopic (UBM) image of a diffuse solid iris stromal mass extending to the angle.

whereas simulating lesions such as metastasis and hemangioma usually show higher internal reflectivity.

B-scan ultrasonography, typically performed with a 10 MHz probe, generates a 2-D image that can be used to evaluate the overall tumor shape, basal dimensions, choroidal excavation, and extrascleral tumor extension, as well as retinal detachment, vitreous and subretinal hemorrhage, and other sequelae (Figure 2A). Intratumoral calcium deposits, which are highly characteristic of retinoblastoma, can be seen as highly reflective foci within the tumor that cast an acoustic shadow into the orbit due to almost complete abrogation of transmitted sound waves. Ultrasound is also useful in retinoblastoma for detecting choroidal invasion, which is an important risk factor for metastasis. Ultrasound can detect

optic nerve invasion, but magnetic resonance imaging (MRI) is generally preferable for making that determination (see below).

Anterior segment high-frequency ultrasonography (HFUS) is a powerful addition to the diagnostic armamentarium. HFUS generates a 2-D image similar to standard B-scan, but it uses much higher sound wave frequencies to provide high resolution imaging of anterior ocular structures. HFUS is particularly useful when evaluating tumors, cysts and other lesions involving the iris, ciliary body, and other anterior segment structures. The first HFUS developed was the 50 MHz ultrasound biomicroscope (UBM) which remains the gold standard for HFUS (Figure 2B). Several advances in UBM technology have occurred in recent years, including development of water bath attach-

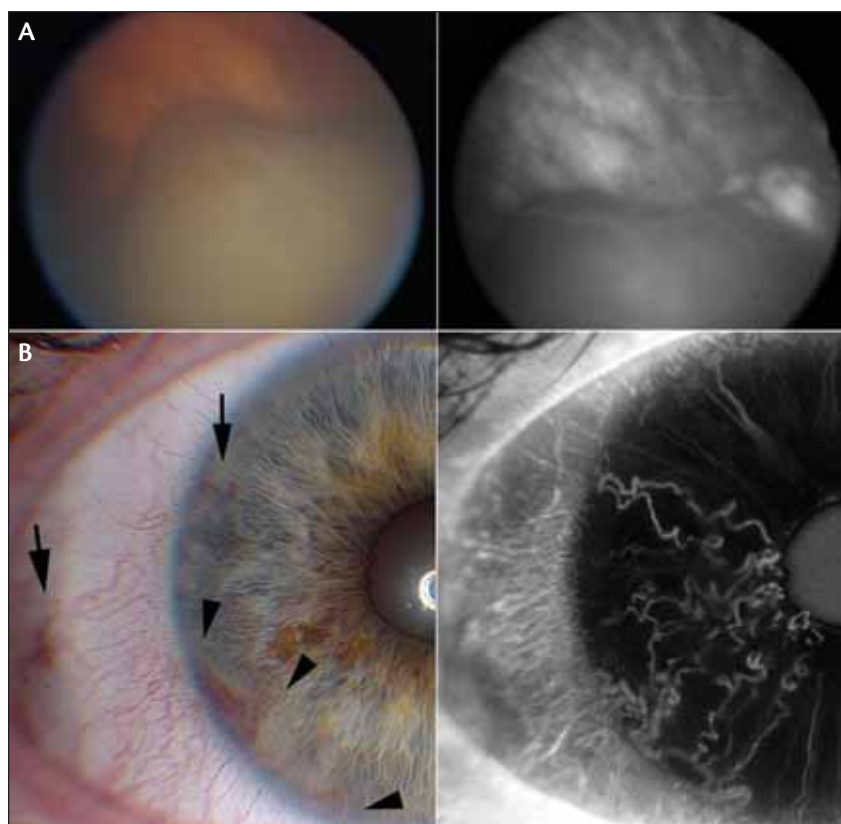


Figure 3. Fluorescein angiography. (A) Color fundus photograph and corresponding fluorescein angiographic image of an eccentric disciform lesion masquerading as a choroidal melanoma. Note the hypofluorescence and absence of intrinsic tumor vascularity, as well as the occult choroidal neovascularization at the upper right margin of the lesion. (B) Color slit lamp photograph and corresponding iris fluorescein angiogram showing an iris arteriovenous malformation mimicking an iris neoplasm. Note the pseudo-sentinel episcleral vessels (arrow) and the margins of the “tumor” (arrow heads) located in the inferotemporal peripheral iris and anterior chamber angle. On angiography, the lesion is clearly seen to be composed of a broad region of iris arteriovenous malformation with no discrete mass.

ments that cover the oscillating tip of the probe and permit contact imaging on seated patients; the development of wide-field image technology that permits individual cross-sectional images up to 18.5 mm long and 14 mm depth; and the development of instruments having interchangeable probes with transducer frequencies ranging from 35 MHz to 80 MHz. A lower-frequency unit (eg, 35 MHz to 40 MHz) that produces wide-field images may be useful to determine the position and relationships of an anterior segment mass in relationship to the crystalline or intraocular lens and the full extent of serous or serosanguinous ciliochoroidal effusions. A higher-frequency unit (eg, 50 MHz to 80 MHz) that images a smaller cross-sectional area is preferred for evaluating structural details of lesions involving the iris and ciliary body. UBM also has

several disadvantages compared to other forms of HFUS. The original UBM unit is still expensive and bulky compared with the other HFUS units. Additionally, it is incompatible with standard A- and B-scan machines, thereby requiring additional office space for the machine. As a result, alternative forms of HFUS have been developed, which employ probes that can be used with standard ultrasound machines. Typically, these probes employ a frequency between 20 MHz and 35 MHz. In most cases, these probes provide adequate imaging at a lower cost and greater convenience than the UBM.

More recently, 3-D ultrasound machines have been developed based on rotation of a sector-scanning transducer. This technology may provide advantages in evaluating intraocular tumors, measuring tumor volume, and localizing radioactive plaques. At the present time, this technology is limited by the significant time delay required for computer acquisition and analysis of the massive amount of data required to generate the 3-D images. Further, it has yet to be shown convincingly that 3-D ultrasound provides significant advantages over standard 2-D B-scans for routine patient care.

OCULAR ANGIOGRAPHY

Two major forms of ocular angiography have been applied to intraocular tumors: fluorescein angiography (FA) and indocyanine green angiography (ICG). Neither of these modalities produces a pattern that is diagnostic of any intraocular tumor. Regardless, they can be useful as ancillary tests in specific circumstances. For example, FA can be useful in diagnosing a uveal melanoma that has hemorrhaged under the retina to produce an appearance similar to a subretinal hematoma, such as can be seen with a retinal arterial macroaneurysm or an eccentric disciform lesion. In the case of a uveal melanoma, the FA will usually show intralesional hyperfluorescence or even frank intrinsic tumor vasculature, whereas a hematoma will block

fluorescence throughout the study and may demonstrate the retinal aneurysm or the occult choroidal neovascularization responsible for an eccentric disciform lesion (Figure 3A). FA can also be useful in evaluating iris tumors and vascular lesions. For example, the intrascleral and iris vessels associated with iris arteriovenous malformation can resemble the sentinel vessels of an iris/ciliary body melanoma, but this distinction is readily made with iris FA (Figure 3B).

ICG is an infrared dye-imaging technique that demonstrates the choroidal vasculature in greater detail than FA. ICG is not as widely used as FA for evaluating intraocular tumors, but it can be superior to FA in a few selected circumstances, such as with choroidal hemangioma, where ICG often demonstrates the classic early lobular filling and late “washout” of dye with a hyperfluorescent rim.

Advances in computer technology now allow high-speed videoangiography to be used on a routine clinical basis. It is yet to be seen whether this new technology will increase the value of FA and ICG in the evaluation of intraocular tumors.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is a powerful technique that generates a high-resolution image from light reflected and transmitted from the tissue of interest in a manner analogous to sound waves used in ultrasonography. OCT has been used most often in ophthalmology for imaging the retina and the retinal pigment epithelium (RPE), but it can be used to image other structures such as the cornea.

OCT is quick, technically easy to perform, noninvasive, comfortable, and safe. It can generate satisfactory images through most media opacities, including vitreous hemorrhage, cataract, and silicone oil (but not gas). The main limitation of OCT in ocular oncology is its limited depth of penetration. In particular, current technology does not allow imaging of the choroid. However, OCT can be useful in several situations. First, it can be used for the evaluation of tumors and tumor-like lesions involving the retina and RPE, such as retinoblastoma, astrocytic hamartoma, combined hamartoma of the RPE and retina, and solitary RPE hamartoma. Second, OCT can help to identify alterations of the retina and RPE that occur as sequelae of intraocular tumors or the treatment of these tumors, including surface-wrinkling maculopathy, macular edema, subretinal fluid, and choroidal neovascularization. Finally, OCT is valuable in characterizing and quantitating localized retinal detachment associated with suspicious choroidal melanocytic tumors (Figure 4). Such localized detachments can be subtle when evaluated by slit-lamp biomicroscopy, so OCT can be helpful in confirming such

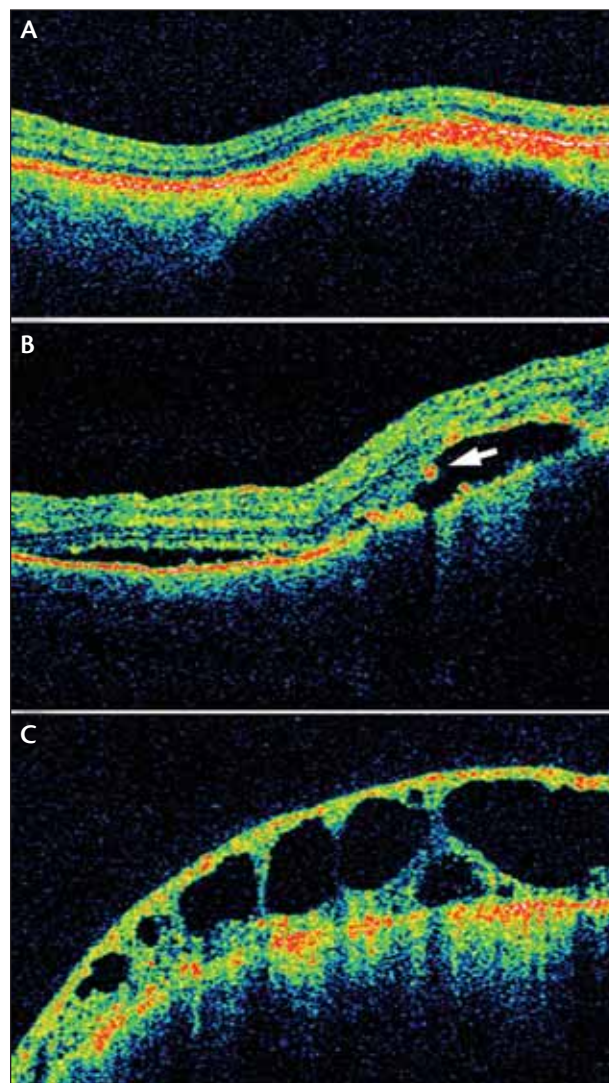


Figure 4. Optical coherence tomography. (A) Normal retinal appearance overlying a choroidal melanocytic tumor. (B) Elevation of the retina overlying a choroidal melanocytic tumor. The retinal layers appear normal with no signs of chronic atrophy. Focal clumps of RPE are evident on the out retinal surface (arrow). These findings are consistent with true serous subretinal fluid in a metabolically active tumor. (C) Elevation of retina overlying a choroidal melanocytic tumor. In this case, the retina is thinned and has undergone cystic degenerative changes, suggesting that the retinal separation is due to chronic atrophic changes in the retina and RPE, rather than true serous subretinal fluid.

a detachment; even more important, OCT can distinguish between active subretinal fluid and chronic atrophic retinal separation. We previously showed that the former is a risk factor for tumor growth, whereas the latter is not.¹ OCT has also been explored for its role in evaluating ante-

rior segment tumors. OCT can be helpful for imaging iris and ciliary body tumors, but in our opinion high frequency anterior segment ultrasound is preferable.

AUTOFLUORESCENCE

Autofluorescent fundus photography takes advantage of the stimulated emission of light from naturally occurring fluorophores within the eye. Autofluorescence can be evaluated using confocal scanning laser ophthalmoscopy (SLO). For example, autofluorescence can be excited by argon blue wavelength (488 nm), and the emitted light detected with a barrier filter. Recent studies have suggested that autofluorescence may be helpful in the evaluation of choroidal melanocytic tumors. Chronic features associated with more benign lesions, such as drusen, RPE hyperplasia, and atrophy, tend to show reduced autofluorescence. In contrast, features associated with high-risk tumors that are more likely to demonstrate growth, such as orange lipofuscin pigmentation and increased size, tend to demonstrate increased autofluorescence. How this modality provides information that cannot be obtained with careful slit-lamp biomicroscopy by a skilled observer, however, remains to be demonstrated.

OCT can be helpful for imaging iris and ciliary body tumors, but in our opinion high frequency anterior segment ultrasound is preferable.

OTHER IMAGING MODALITIES

Computed tomography (CT), MRI, and positron emission tomography (PET) can be useful in the evaluation of intraocular tumors in selected circumstances. CT can be helpful in confirming the diagnosis of retinoblastoma when there is diagnostic uncertainty. The presence of intratumoral calcium, particularly in patients under 2 years old, is highly consistent with retinoblastoma rather than simulating lesions such as Coats disease. CT also is helpful for ruling out optic nerve or orbital invasion and for evaluating the intracranial midline for the presence of "trilateral" retinoblastoma. When the diagnosis of retinoblastoma is not in doubt, however, MRI is preferred over CT to avoid unnecessary radiation exposure in patients with a hereditary predisposition to second primary cancers.

Whole-body PET with [¹⁸F]-fluoro-2-deoxy-glucose, especially when combined with CT (PET-CT), is a powerful tool in the systemic screening of patients at high suspicion of harboring metastatic disease. Several investigators have stud-

ied the use of PET in evaluating primary intraocular tumors, but, to date, the utility of PET in this setting is unproven.■

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1. Espinoza G, Roseblatt B, Harbour JW. Optical coherence tomography in the evaluation of retinal changes associated with suspicious choroidal melanocytic tumors. *Am J Ophthalmol.* 2004;137(1):90–95.

Suggested Reading

1. Augsburger JJ, Affel LL, Benarosh DA. Ultrasound biomicroscopy of cystic lesions of the iris and ciliary body. *Trans AM Ophthalmol Soc.* 1996;94:259–271.
2. Beyer T, Pietrzyk U, Knoess C, et al. Multi-modality imaging of uveal melanomas using combined PET/CT, high-resolution PET and MR imaging. *Nuklearmedizin.* 2008;47(2):73–79.
3. Brisse HJ, Guesmi M, Aerts I, et al. Relevance of CT and MRI in retinoblastoma for the diagnosis of postlaminar invasion with normal-size optic nerve: a retrospective study of 150 patients with histological comparison. *Pediatr Radiol.* 2007;37(7):649–656.
4. Collet LC, Pulido JS, Gunduz K, et al. Fundus autofluorescence in choroidal metastatic lesions: a pilot study. *Retina.* 2008;28(9):1251–1256.
5. Gunduz K, Pulido JS, Bakri SJ, Petit-Fond E. Fundus autofluorescence in choroidal melanocytic lesions. *Retina.* 2007;27(6):681–687.
6. Lavinsky D, Belfort RN, Navajas E, et al. Fundus autofluorescence of choroidal nevus and melanoma. *Br J Ophthalmol.* 2007;91(10):1299–1302.
7. Mansouri K, Sommerhalder D, Shaarawy T. Prospective comparison of ultrasound biomicroscopy and anterior segment optical coherence tomography for evaluation of anterior chamber dimensions in European eyes with primary angle closure. *Eye.* 2009 May 15. [Epub ahead of print]
8. Miller NR. Primary tumours of the optic nerve and its sheath. *Eye.* 2004;18(11):1026–1037.
9. Pavlin CJ, Vasquez LM, Lee R, et al. Anterior segment optical coherence tomography and ultrasound biomicroscopy in the imaging of anterior segment tumors. *Am J Ophthalmol.* 2009;147(2):214–219 e2.
10. Peyster RG, Augsburger JJ, Shields JA, Hershey BL, Eagle R Jr, Haskin ME. Intraocular tumors: evaluation with MR imaging. *Radiology.* 1988;168(3):773–779.
11. Piccolino FC, Borgia L, Zinicola E. Indocyanine green angiography of circumscribed choroidal hemangiomas. *Retina.* 1996;16(1):19–28.
12. Schmidt GP, Kramer H, Reiser MF, Glaser C. Whole-body magnetic resonance imaging and positron emission tomography-computed tomography in oncology. *Top Magn Reson Imaging.* 2007;18(3):193–202.
13. Schmitz-Valckenberg S, Holz FG, Bird AC, Spaide RF. Fundus autofluorescence imaging: review and perspectives. *Retina.* 2008;28(3):385–409.
14. Yannuzzi LA, Ober MD, Slakter JS, et al. Ophthalmic fundus imaging: today and beyond. *Am J Ophthalmol.* 2004;137(3):511–524.