Iris and iridociliary melanoma : concepts in diagnosis and management

Razzaq, L.

Chapter 3

Anterior segment imaging for iris melanocytic tumors

Lubna Razzaq, Katinka Emmanouilidis-van der Spek,
Gregorius P.M. Luyten, Rob J.W. de Keizer

Department of Ophthalmology, Leiden University Medical Center (LUMC),
Leiden, the Netherlands.

European Journal of Ophthalmology, 2011;21(5): 608-614

Abstract

Purpose: To determine the role of anterior segment Optical Coherence Tomography (AS-OCT) and other anterior segment imaging techniques (Pentacam and Slit lamp-OCT) for analysis of iris melanocytic tumors and to compare results with clinical features and ultrasound biomicroscopy (UBM).

Methods: Between 2006 and 2009, sixty-one patients with melanocytic iris tumors were examined using a variety of anterior segment imaging techniques, i.e. Pentacam, Slit lamp-OCT (SL-OCT), Anterior segment OCT (AS-OCT) and UBM (50MHz). Pentacam was performed in 17 patients, SL-OCT in 12, AS-OCT in 46 and UBM in 49 patients.

Results: The Pentacam images identified the tumor in three of 17 patients (18%), SL-OCT in eight of 12 (67%) and AS-OCT in 44 of 46 patients (96%). AS-OCT results were compared with UBM in 42 patients: in 86% of these, the results were comparable, although AS-OCT demonstrated a ciliary body extension of iris tumors in only one out of three cases analyzed.

Conclusion: Iris melanocytic tumors were located by AS-OCT in 96% of cases and results were comparable to UBM imaging, while both SL-OCT and Pentacam were less reliable for detecting and measuring anterior segment lesions. AS-OCT gives precise anterior eye segment diameters, which are useful for calculating brachytherapy dosage using a module developed at the LUMC. Therefore, AS-OCT is a reliable, convenient and non-contact method for demonstrating and measuring pure iris tumors, but UBM is superior in detecting a ciliary body extension of these tumors.

Introduction

Melanocytic lesions of the iris consist mostly of naevi and melanoma. Iris naevi are present in 4 - 6% of Caucasians while iris melanoma accounts for less than 10% of all uveal melanomas [1,2]. The diagnosis of iris naevi and melanomas is made clinically (tumor prominence, satellite lesions, diffuse extension and growth, and dispersion in the anterior chamber angle) and by anterior segment imaging. Imaging of anterior segment tumors has traditionally been the domain of ultrasound. The development of ultrasound biomicroscopy (UBM) using 50 MHz has improved the diagnosis of anterior segment lesions and UBM has become the standard in defining the extent of pigmented lesions of the anterior segment. Structures seen on UBM have been compared extensively to clinical findings, traditional ultrasound images, and histological findings, which ensures correct diagnosis and intralesional details with this technique [3]. Disadvantages of UBM are that it requires water bath immersion of the eye, which is unpleasant, time-consuming and requires a skilled examiner. Recently, new technologies offering the possibility of non-contact cross-sectional imaging of the cornea and whole anterior segment have become commercially available. These new approaches, based on rotating Scheimpflug imaging (Pentacam) and anterior segment optical coherence tomography (AS-OCT), supplement the more established modalities of corneal topography and ultrasound biomicroscopy [4]. Pentacam provides sharp and crisp images from the anterior corneal surface to the posterior crystalline lens. In the last decade, OCT has been introduced for high-resolution imaging of the retina. In principle, OCT is similar to UBM, but detects infrared light reflected from the tissues, instead of sound waves. It is a non-contact imaging technology that provides detailed cross-sectional images of internal structures in biological tissues [5]. Over the last few years, AS-OCT has been developed for high resolution imaging of the anterior segment. AS-OCT is similar to OCT but works at 1310 nm wavelength, with 4000 axial scans per second, which allows deeper penetration through the highly-reflective tissue of the sclera, and reduces the retinal exposure [6]. It was tested and compared with UBM and slit- lamp photography and has been shown to be accurate and repeatable for anterior segment biometry [7,8]. Anterior segment OCT has many advantages compared to other imaging techniques, such as its non-contact nature, convenience, high resolution and wide field of frame captured at one point [9]. The depth resolution of AS-OCT is higher (8 -15 μm) than UBM (25μm), resulting in more detailed images. The scan depth is 3 to 6 mm depending on the scan type. The lateral resolution of AS-OCT is 40-50 μm which is about the same as for UBM [10]. AS-OCT performs 256 A scans in 125 ms for a low-resolution image, or 512 A scans in 250 ms for a high resolution

image [11]. The AS-OCT reflectivity characteristic of tissue correlates with the degree of pigmentation and scattering, enabling a more intuitive interpretation than with UBM. AS-OCT also facilitates frequent imaging because of its non-contact nature, which can be used to monitor the growth of the tumor, which is very important since growth over time is an indication of malignancy. Slit-lamp OCT is an OCT machine adapted to work with a slit-lamp, so that while viewing the lesion with a slit-lamp, an OCT image can be taken.
In our study, we evaluated the usefulness of Pentacam, SL-OCT and AS-OCT for imaging iris melanocytic tumors and compared the results with clinical findings and UBM.

Materials and Methods

Sixty-one patients with melanocytic iris tumors, who were referred to the Ocular Oncology unit of the LUMC between January 1998 and December 2009, were included in this study. All patients were (re)examined with Pentacam, SL-OCT and AS-OCT between October 1, 2006 and December 31, 2009. Diagnosis of the iris melanocytic tumors was based on clinical features and UBM, and results of all imaging techniques were compared with these findings, where available. All the patients were informed and their consent was obtained to undergo examinations with different imaging techniques according to the guidelines of the Helsinki Declaration.
The Pentacam developed by Oculus (Germany) is a 360° rotating Scheimpflug camera, which captures Scheimpflug images of the anterior eye segment. The Pentacam has a high resolution 1.5 Megapixel camera that uses a blue light emitting diode (475 nm UV-free) with a speed of 50 images in two seconds.
Slit-lamp OCT, marketed by Heidelberg Engineering (Germany), uses a light source of super-luminescent light - emitting diode with a wavelength of 1300 nm. Scan width is variable with 2, 4, 8 and maximum of 15 mm. Scan depth is 7 mm and the scan speed is 200Hz. We used SL-OCT in 2007 for research purposes with version 1 of its software and in 2008 with version 2.
Anterior segment OCT (Visante OCT) was developed by Carl Zeiss Meditec, Inc. (Dublin, California). Its wavelength is 1310 nm. It uses 5.0 mW of power and its speed is 4 to 8 frames per second. The AS-OCT has an internal fixation target with accommodation control. Wide-field frames were processed with automated software to correct for refraction at the air-corneal interface. Unlike SL-OCT, It has a screen on which the examiner can view the eye and lesion. Images were taken in both normal and high resolution modes.
Until 2007, in the Netherlands, Ultrasound biomicroscopy (UBM) was available

in Nijmegen only; it was performed with a 50-MHz probe manufactured by Humphrey Instruments (California, USA). In 2007, the Lin 50 UBM probe, manufactured by Quantel Medical Aviso (France), became available at the LUMC and thereafter UBM examination was performed at the LUMC. In 12 of 49 patients, UBM was performed in Nijmegen (24%), while the remaining 37(76%) examinations were done in Leiden. Subjects were examined in the supine position with the eye immersed in saline solution by using an eyecup. UBM image size was 5 mm wide and 5 mm deep. Both longitudinal and transverse scans were made with the tumor focused perpendicularly. Multiple scans were obtained and measurements were averaged.

The results of all imaging techniques were categorized as very good, good, moderate and bad. The categories were based on the following parameters: 1. the iris tumor could be located; 2 tumor structural details were visible including the integrity of iris pigment epithelium; 3. the dimensions of the lesion could be measured including iris thickness and tumor prominence; 4. tumor location and extension in the anterior chamber angle could be visualized and 5. the ciliary body could be visualized. The results were considered very good when all of the five criteria were met and the images were even better than UBM images. They were considered good when the ciliary body could not be visualized but criteria 1, 2, 3 and 4 were met. The results were moderate when only criterion 1 was met. They were considered bad when none of the criteria were met and the tumor was not located with the imaging technique although it was present clinically and on UBM.

The images of the iris tumors from 49 patients were compared with UBM with reference to quality of the image, tumor measurements including thickness, structure, reflectivity and extension of the lesion into the ciliary body or anterior chamber, and classified as equal or inferior to UBM. The difference between mean thickness of iris naevi and melanoma measured by UBM and AS-OCT was calculated using the paired t-test. As UBM was not available at the LUMC till 2007, a few cases with the iris naevi not extending in the ciliary body did not have the UBM examination.

Results

Sixty-one patients were examined (46% female, 54% male) with a mean age of 61 years (range 21-84 years). The clinical diagnosis varied from iris naevus in 39 patients (64%) and suspected melanoma of the iris and / or ciliary body in 22 (36%) (Table 1). Of the 61 patients, 17 patients were examined with Pentacam, 12 with SL-OCT and 46 with AS-OCT. The results of these techniques were compared with UBM in 49 patients. The color of the eyes ranged from grey to grey green in 60 patients (97%), while only 2 eyes were brown.

Table 1 Numbers of iris tumors examined by different anterior segment imaging techniques

Diagnosis	Pentacam n=17	SL-OCT n=12	AS-OCT n=46	UBM n=49
Iris Naevus n=39	11	7	32	28
Iris and/or anterior ciliary body melanoma n=22	6	5	14	21

Iris naevi

In total, 39 patients with iris naevi were included in our study of which 32 were examined with AS-OCT, seven with SL-OCT and eleven with Pentacam. The images of these techniques were compared with UBM in 28 patients. The results of AS-OCT were much better than of SL-OCT and Pentacam. Image of an iris naevi with Pentacam and SL-OCT is shown in Figure 1 & 2.
A comparison of AS-OCT results with UBM in 28 of these patients showed that both techniques were equal in all of these cases. Mean tumor thickness measured by UBM was 0.86 mm (range: 0.47 -1.61) and was also 0.86 mm (range: 0.48 -1.60) by AS-OCT (p-value: 0.65, 95% CI: -0.0075 -0.0048). Pentacam and SL-OCT results were compared with UBM in six and five patients, respectively, and Pentacam was inferior to UBM in all the cases while SL-OCT was equal to UBM in one case.

Iris and/or ciliary body melanoma

Twenty-two patients with suspected iris and/or anterior ciliary body melanoma were included in our study of which 14 were examined with AS-OCT, five with SL-OCT and six with Pentacam (Table 2). AS-OCT showed the best results.
AS-OCT was equal to UBM in eight out of 14 patients. Mean tumor thickness

Figure 1 Pentacam image of an iris naevus present in the inferior quadrant of the iris. The arrow in the picture shows the location of the iris naevus. The angle measurements are also shown i.e. 26.5° at 12 o'clock and 29.2° at 6 o'clock

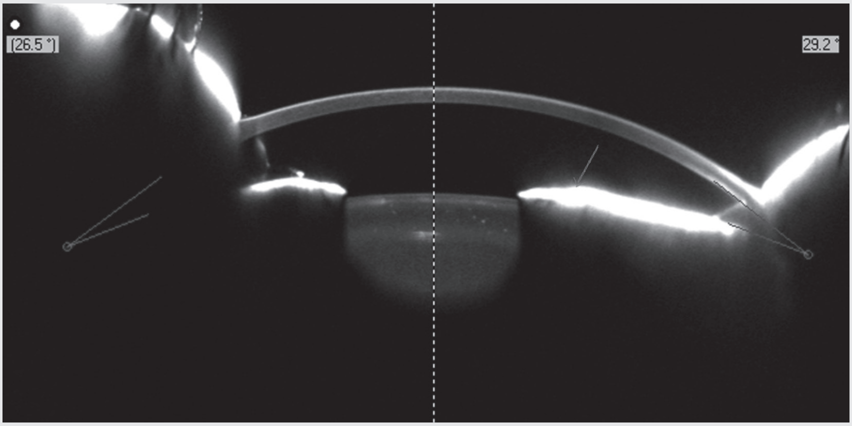


Figure 2 SL-OCT image of an iris tumor with prominent pupillary sphincters

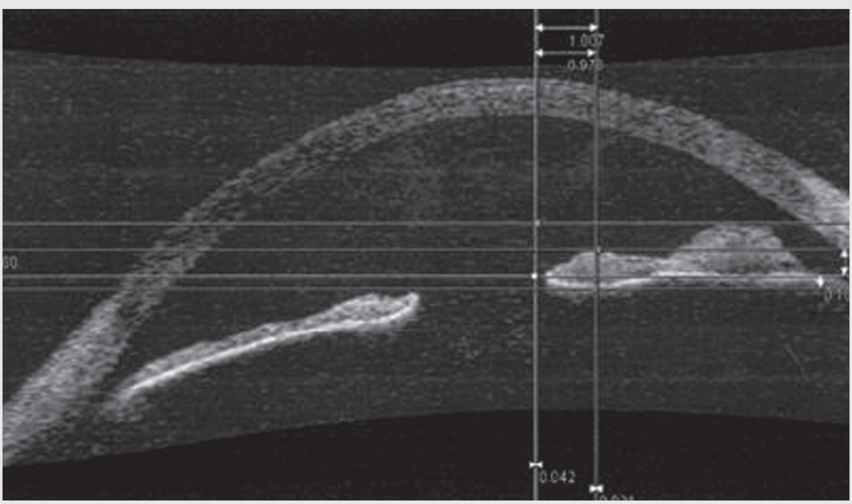


Table 2 Results of Pentacam, SL-OCT and AS-OCT

Examination	Very Good (%)	Good (%)	Moderate (%)	Bad (%)
Pentacam (n)				
Iris naevus (11)	0	1 (9)	2 (18)	8 (73)
Iris/CB melanoma (6)	0	0	0	6 (100)
Total (17)	0	1 (6)	2 (12)	14 (82)
SL-OCT (n)				
Iris naevus (7)	0	4 (57)	2 (29)	1 (14)
Iris/CB melanoma (5)	0	2 (40)	0	3 (60)
Total (12)	0	6 (50)	2 (17)	4 (33)
AS-OCT (n)				
Iris naevus (32)	7 (22)	25 (78)	0	0
Iris/CB melanoma (14)	2 (14)	7 (50)	3 (22)	2 (14)
Total (46)	9 (20)	32 (70)	3 (6)	2 (4)

measured by UBM in these patients was 2.04 mm (range: 1.08 - 3.02) and by AS-OCT 2.01 mm (range: 1.08 - 3.00) (p-value: 0.11, 95% CI: -0.0063 - 0.0520). The results of Pentacam and SL-OCT were inferior to UBM in all patients compared. A summary of the results is provided in Table 3.

Table 3 Comparison of results of Pentacam, SL-OCT and AS-OCT to results obtained by UBM

Examination	Equal to UBM (%)	Inferior to UBM (%)
Pentacam (n)		
Iris naevus (6)	0	6 (100)
Iris/CB melanoma (6)	0	6 (100)
Total (12)	0	12 (100)
SL-OCT (n)		
Iris naevus (5)	1 (20)	4 (80)
Iris/CB melanoma (5)	0	5 (100)
Total (10)	1 (10)	9 (90)
AS-OCT (n)		
Iris naevus (28)	28 (100)	0
Iris/CB melanoma (14)	8 (57)	6 (43)
Total (42)	36 (86)	6 (14)

The results of each imaging technique with regard to identifying tumor location, dimensions, chamber angle extension and ciliary body extension are shown in Table 4. SL-OCT was not able to locate the extension of lesion to ciliary body in any of the patients. AS-OCT showed a pigment layer arising from the tumor and attaching to the Descement's membrane in three patients, which was seen only after detailed gonioscopy and could not be found with UBM. Like SL-OCT, it was not possible to visualize ciliary body extension of the lesions with AS-OCT and in only one out of three patients ciliary body extension could be visualized.

Table 4 Results of each technique showing their ability to determine tumor location, dimensions, chamber angle extension and ciliary body extension

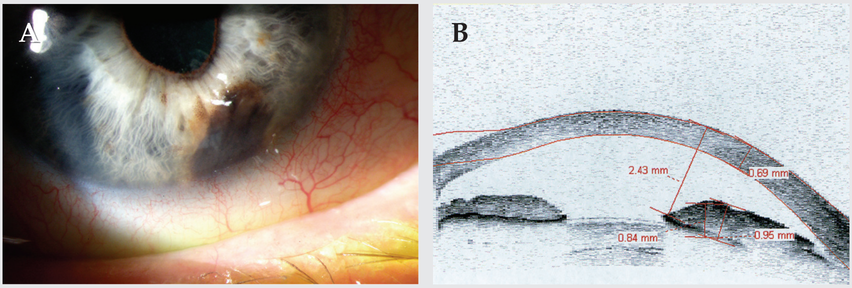
Examination	Location of tumor (%)	Dimensions of tumor (%)	Chamber angle extension (%)	Ciliary body extension n=3(%)
Pentacam (17)	3 (18)	1 (6)	0	0
SL-OCT (12)	8 (67)	6(50)	0	0
AS-OCT (46)	44 (96)	41(90)	41 (90)	1 (33)

Discussion

This study evaluated the role of different anterior segment imaging techniques, especially AS-OCT, in demonstrating iris melanocytic tumors. At the start of this study in 2006, little was known about the potential of imaging of iris tumors with these modalities. We compared Pentacam, SL-OCT and AS-OCT images with clinical findings and UBM, which is considered the standard for anterior segment lesions, although the sensitivity of UBM for such tumors is not as high as for choroidal melanomas. As AS-OCT uses light, it does not require fluid immersion or direct probe contact. This makes it easier to use providing a high patient compliance. We now have used AS-OCT for many other lesions of the iris, such as iris cysts, iris atrophy, iris metastases and Lisch nodules, but we did not include these in the current study because of the diversity of diagnoses. The limitation of our study is the small number of patients examined with SL-OCT and Pentacam, due to a limited availability of these machines for research

purpose only. The strength of this study is the fairly large number of patients examined with AS-OCT as well as with UBM.
The results of AS-OCT were encouraging, as we were able to localize lesions in 96% of the patients. Findings were comparable to UBM with regard to defining location, prominence, structure and extension into anterior chamber. Details were easily visible, especially if the high resolution mode was used. Moreover, precise tumor measurements were obtained which are essential for the radiation dose calculation for the prospective treatment with plaque brachytherapy (Figure 3 A & B). These results are comparable to the literature on imaging of iris tumors with AS-OCT [12]. Another important point is that the contrast of iris features on AS-OCT correlates with pigmentation. In the normal iris, the stroma has a medium reflectivity and the anterior stroma has a higher reflectivity. The iris pigment epithelium forms a highly reflective posterior boundary of the iris. Ectropion uveae appears as a highly reflective anterior surface at the pupillary margin. Melanotic lesions have a higher reflectivity while amelanotic lesions have a reflectivity similar to or lower than stroma. In this study, iris naevi showed a high reflectivity and shadowing of the pigment epithelium while the iris melanoma had variable reflective areas, distributed throughout the whole thickness of the mass. These reflectivity patterns may be of diagnostic value, while UBM shows medium to low reflectivity for all iris naevi and melanomas, independent of degree of pigmentation [13]. However, 97% of the eyes that we examined were grey to grey-green and the reflectivity patterns can be different in brown eyes, as we found in two brown eyes examined. So, further research is needed to assess the diagnostic reliability of AS-OCT to differentiate between iris naevi and melanoma in different eye colors.
A major limitation of the AS-OCT found in this study was that even at a wavelength of 1.3 micron visualization of the ciliary body was possible in only one out of three cases with ciliary body involvement. Therefore, UBM remains superior if ciliary body extension of an iris tumor is suspected. Another limitation of AS-OCT is that the posterior boundary of heavily-pigmented lesions greater then 2.5 mm becomes blurred.
The results of SL-OCT were good in 50% of the patients, but the image details were less visible than with AS-OCT. Results of SL-OCT were comparable to UBM in only one patient. The results of Pentacam were bad in most of the cases (82%).
This study illustrates the role of the anterior segment OCT in imaging iris naevi and iris melanoma. AS-OCT is a non-contact technique, which makes it possible to measure iris lesions accurately, especially the perpendicular diameters which are useful for the brachytherapy dosage calculation module developed at the LUMC [14]. The results obtained with other anterior segment imaging techniques

Figure 3 (**A**) Iris melanoma present in the inferior quadrant of the iris from 4-6 o'clock in one of the study patients (**B**) AS-OCT image of the same tumor showing tumor dimensions with and without corneal thickness



such as Pentacam and SL-OCT were not encouraging. On the basis of our results we recommend the use of AS-OCT to detect measure and monitor the growth of iris melanocytic tumors once extension into the ciliary body has been ruled out by UBM.

Conclusion

AS-OCT is advancement in imaging iris melanocytic tumors but its usefulness is limited by its inability to visualize the ciliary body extension of these tumors. Therefore, UBM remains the preferred choice for imaging the majority of anterior segment tumors.

Acknowledgements
The authors thank Carl Zeiss Meditec (California) and Heidelberg (Germany) for providing AS-OCT and SL-OCT free of charge for research purposes; and Dr. A.M. Verbeek and Prof. Dr. J.E.E. Keunen (Nijmegen University Medical Center, Nijmegen) for performing the UBM examinations for initial part of this study.

References

1. Harbour JW, Brantley MA, Hollingsworth H, Gordon M. Association between posterior uveal melanoma and iris freckles, iris naevi, and choroidal naevi. *Br J Ophthalmol* 2004;88(1): 36-38.
2. Egan KM, Seddon JM, Glynn RJ, Gragoudas ES, Albert DM. Epidemiologic aspects of uveal melanoma. *Surv Ophthalmol* 1988;32: 239-51.
3. Silverman RH, Cannata J, Shung KK, et al. 75 MHz ultrasound biomicroscopy of anterior segment of eye. *Ultrason Imaging* 2006;28: 179-88.
4. Konstantopoulos A, Hossain P, Anderson DF. Recent advances in ophthalmic anterior segment imaging: a new era for ophthalmic diagnosis? *Br J Ophthalmol* 2007;91: 551-57.
5. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science* 1991;254: 1178-81.
6. Nubile M, Calienno R, Lanzini M, Mastropaqua L. Discovering clinical applications for Visante OCT. *Cataract and refractive surgery today Europe* 2008; March:38-41.
7. Chalita MR, Li Y, Smith S, et al. High- speed optical coherence tomography of laser iridotomy. *Am J Ophthalmol* 2005;140: 1133-36.
8. Goldsmith JA, Li Y, Chalita MR, et al. Anterior chamber width measurement by high-speed optical coherence tomography. *Ophthalmology* 2005;112(2): 238-44.
9. Huang D, Li Y, Radhakrishnan S. Optical coherence tomography of the anterior segment of the eye. *Ophthalmol Clin North Am* 2004;17: 1-6.
10. Bakri SJ, Sculley L, Singh AD. Imaging techniques for uveal melanoma. *Int Ophthamol Clin* 2006;46: 1-13.
11. Pavlin CJ, Vásquez LM, Lee R, Simpson ER, Ahmed II. Anterior segment optical coherence tomography and ultrasound biomicroscopy in the imaging of anterior segment tumors. *Am J Ophthalmol* 2009;147: 214-19.
12. Singh AD, Wackernagel W, Rao NA, Steinert RF. Optical coherence tomography for anterior segment tumours. *Anterior segment optical coherence tomography*. 1st ed. Thorofare: SLACK Incorporated: 2008; 129-30.
13. Pavlin CJ, McWhae JA, McGowan HD, Fostor FS. Ultrasound biomicroscopy of anterior segment tumours. *Ophthalmology* 1992;99: 1220-28.
14. Razzaq L, Keunen JE, Schalij-Delfos NE, Creutzberg CL, Ketelaars M, de Keizer RJ. Ruthenium plaque radiation therapy for iris and iridociliary melanomas. *Acta Ophthalmol* 2010; Jul 29. [Epub ahead of print]