

Treatment Outcome of Acquired Retinal Pigment Epithelial Tumors with Rhuthenium-106 Plaque Radiotherapy: Experience on Two Cases

Masood Naseripour¹, Ahad Sedaghat¹, Parya Abdolalizadeh¹, Ehsan Azizi¹

¹Eye Research Center, The Five Senses Institute, Rassoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

Abstract

Purpose: To report the clinical outcome of rhuthenium-106 plaque radiotherapy in acquired retinal pigment epithelial (RPE) tumors.

Methods: In this interventional case series, two eyes of two patients with clinically diagnosed ocular-acquired RPE tumors including adenoma and adenocarcinoma underwent plaque radiotherapy with rhuthenium-106. The clinical findings and visual outcome of the patients were evaluated.

Results: The first patient was a 44-year-old male, and the second was a 32-year-old female. The follow-up times were 24 and 32 months. The tumor was unilateral and hyperpigmented in both cases, located at juxtapapillary in one patient and on peripheral part of the retina in the other. Vitreous hemorrhage and peripheral exudation were obvious in one patient. Macular edema, epiretinal membrane, and retinal feeder vessels were also detected in the examination. The patients underwent plaque radiotherapy with rhuthenium-106 as the first step of management. The tumor has been stable until the last follow-up in both patients with globe preservation and acceptable visual acuity (5/10 for the first case and 4/10 for the second case).

Conclusion: Rhuthenium-106 plaque radiotherapy might be a conservative therapy in the management of acquired RPE tumors and prevent early enucleation.

Keywords: Ocular oncology, Retinal pigment epithelium, Retinal pigment epithelium adenoma, Rhuthenium-106 plaque radiotherapy

Address for correspondence: Ahad Sedaghat, Eye Research Center, The Five Senses Institute, Rassoul Akram Hospital, Sattarkhan Niayesh Street, Tehran 1455364, Iran.

E-mail: ahad_s2000@yahoo.com

Submitted: 21-Jun-2019; **Revised:** 30-Dec-2019; **Accepted:** 11-Apr-2020; **Published:** 04-Jul-2020

INTRODUCTION

Acquired tumors of the retinal pigment epithelium (RPE), including adenoma and adenocarcinoma, are an exceedingly rare intraocular tumor, usually diagnosed in adulthood, with an age range of 26–80 years at the time of diagnosis and no obvious gender dominance.¹⁻³ Clinical differentiation between adenoma and adenocarcinoma is generally difficult and made based on the pathology.²

There is no accepted algorithm for the management of acquired RPE tumors. They are usually confined to the orbit and do not

metastasize despite histopathological features of invasion. They are also clinically misdiagnosed with choroidal melanoma. Therefore, some ocular oncologists prefer enucleation to achieve definite diagnosis and treatment.⁴⁻⁸ However, limited trials of other modalities such as local tumor resection,⁹⁻¹¹ laser photocoagulation,¹² cryotherapy,^{3,12,13} radiation,^{3,11} and a combination of them have also been reported to preserve the globe and a trend away from enucleation as much as possible. In this study, we report our experience of two patients with

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Naseripour M, Sedaghat A, Abdolalizadeh P, Azizi E. Treatment outcome of acquired retinal pigment epithelial tumors with rhuthenium-106 plaque radiotherapy: Experience on two cases. *J Curr Ophthalmol* 2020;32:297-301.

Access this article online

Quick Response Code:



Website:
www.jcurrophthalmol.org

DOI:
10.4103/JOCO.JOCO_144_20

acquired RPE tumors who were managed by ruthenium-106 plaque radiotherapy as a globe preservation approach.

CASE REPORT

Medical records of patients with acquired RPE tumors who were referred to the ophthalmology clinic at a university-based hospital (Rassoul Akram Hospital, Tehran, Iran) or senior author's (M.N.) private clinic were reviewed from August 2016 to October 2019. This study adhered to the tenets of the Declaration of Helsinki and informed consent was obtained from two patients. The diagnosis of RPE tumors was done based on the clinical features, funduscopy examination, and results of ancillary tests including A-scan, B-scan, fluorescein angiography, and optical coherence tomography (OCT). Two patients underwent plaque radiotherapy with ruthenium-106 as the first step of management. Patients underwent comprehensive ophthalmologic examination, including best corrected visual acuity (BCVA), funduscopy, and intraocular pressure measurement in follow-up visits as well as ancillary tests to confirm the stability or regression of the lesion.

Table 1 shows the overview of two cases explained below.

Case 1

A 44-year-old male was referred to our clinic in August 2016 for a progressive loss of vision in his left eye from 4 months earlier. His visual acuity was 10/10 OD and 5/10 OS. Intraocular pressure was normal in both eyes. Examination of the right eye was not contributory. Funduscopy showed resolving vitreous hemorrhage and related media haziness that prevented well evaluation of the fovea and hyperpigmented mass in supranasal quadrant, 5 mm away from the disc. There was no obvious feeder vessel. The tumor dimensions were 7 mm × 6 mm in size and 4.95 mm in maximum height [Figure 1a]. Fluorescein angiography revealed early hypofluorescence, late mottle hyperfluorescence areas in the lesion, and petaloid pattern in fovea [Figure 2]. OCT confirmed cystoid macular edema. The ultrasonography showed dome-shaped solid mass with medium-to-high internal reflectivity and no choroidal excavation. The patient underwent plaque radiotherapy with ruthenium-106 after 5 months because the patient refused treatment for a while. The BCVA was 3/10 in 3 months after plaque radiotherapy. The thickness of the tumor was 4.91 mm. Due to persistent vitreous hemorrhage and cystoid macular edema, intravitreal bevacizumab was injected two times. After

24 months follow-up, the vision was 5/10, and tumor thickness decreased to 3.37 mm [Figure 1b].

Case 2

A 32-year-old woman presented with a complaint of progressive visual loss of the left eye from 8 months earlier. The examination of the right eye was within the normal limit. The BCVA of the left eye was 4/10. In the left posterior segment examination, there was a hyperpigmented mass with obvious large feeder vessels surrounded by extensive exudates in the supratemporal quadrant [Figure 3a]. Epiretinal membrane was another finding. The tumor size was 7 mm × 7 mm, and maximum thickness was measured 5.5 mm. Ultrasonography revealed solid dome-shaped mass with medium-to-high internal reflectivity. The fluorescein angiography showed large tortuous retinal feeder vessels without leakage [Figure 3b]. Plaque radiotherapy with ruthenium-106 was done. After 7 months, the exudation was completely absorbed, and the tumor regressed. The final BCVA remained 1/10 [Figure 4a-c]. Later, the patient developed radiation retinopathy and central macular edema, whereas the thickness of the tumor reduced to 3 mm after 32 months of plaque radiotherapy.

DISCUSSION

Most cases of acquired RPE tumors represent a diagnostic dilemma for the clinician since they may masquerade as choroidal malignant melanoma.^{4,6,10,13,14} Since tumors of the RPE have no potential for metastasis, and the treatment of these entities may differ, it would be desirable to identify the specific features of each lesion [Table 2]. On the other hand, RPE tumors can rarely mimic a choroidal hemangioma with slowly progression.⁸ It is also difficult to differentiate acquired RPE tumors from other proliferative conditions of

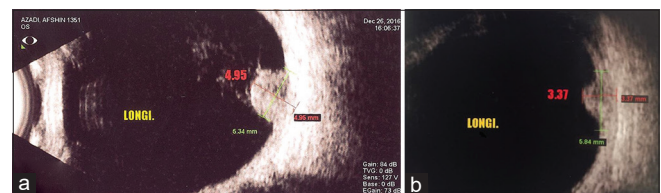


Figure 1: On B-scan ultrasound image of the left eye of the Case 1: paraxial section shows nodular, highly reflective fundus mass that had a thickness of 4.95 mm before plaque radiotherapy (a) decreasing to 3.37 mm, 24 months after plaque therapy (b)

Table 1: Demographic and clinical features of two patients with acquired retinal pigment epithelial tumors

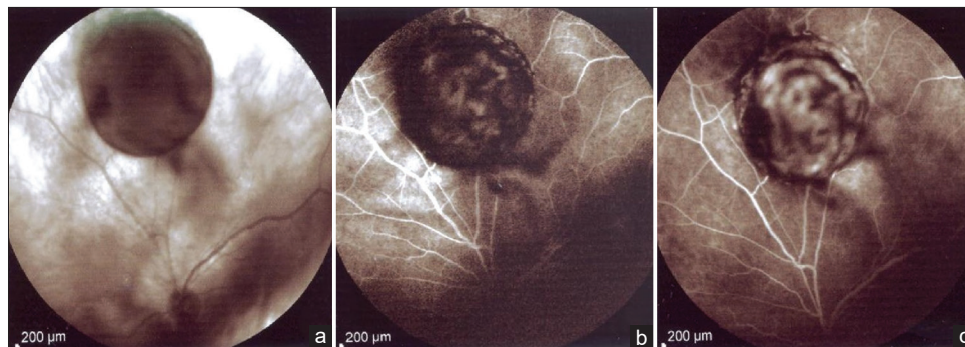
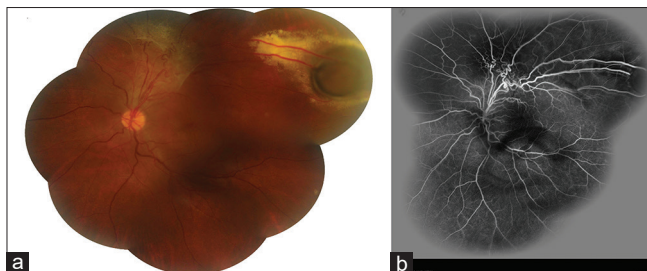
Patient number	Age	Sex	Years of diagnosis	Initial BCVA	Last BCVA	Duration of follow-up	Location of tumor	Initial thickness	Final thickness	Associated findings	Management
1	44	Male	2016	5/10	5/10	24 months	Juxtapapillary	4.5	3.5	Vitreous hemorrhage, macular edema	Plaque therapy, IVB
2	32	Female	2017	4/10	4/10	32 months	Supratemporal quadrant in the periphery	5.5	3	Peripheral exudation, feeder vessels, ERM	Plaque therapy, IVB

BCVA: Best corrected visual acuity, IVB: Intravitreal bevacizumab, ERM: Epiretinal membrane

Table 2: Comparing different characteristics of choroidal melanoma and acquired retinal pigment epithelial tumors

	Melanoma	Acquired RPE tumors
Dark black color	Sometimes	Usual
Surrounding pigmented choroidal base	Usual	Rare
Dilated vessel type	Veins	Artery and vein
Extensive exudate	Rare	Usual
Exudative retinal detachment	Serous	Yellow exudate
Pattern of fluorescein angiography	Earlier hyperfluorescence and late intense staining	Early hypofluorescence and late spot-like staining
Choroidal blood supply (double circulation in fluorescein angiography)	Usual	Rare
Internal reflectivity in A-scan	Low	High
Mushroom shape in B-scan	Usual	Rare
Peripheral margin in B-scan	Sloping	Abruptly elevated
Acoustic hollowness in B-scan	Usual	Rare
Systemic metastasis	Usual	Rare

RPE: Retinal pigment epithelium

**Figure 2:** Fluorescein angiography of the left eye of Case 1 at early (a), mid (b), and late (c) phases, demonstrating early hypo and late patchy hypofluorescent and hyperfluorescent retinal pigment epithelium alterations**Figure 3:** Color fundus photography (a) and fluorescein angiography (b) of the left eye of Case 2 which shows a pigmented mass with feeder vessels in supratemporal quadrant

the RPE such as congenital hypertrophy RPE (CHRPE) and reactive hyperplasia. Although acquired RPE tumors, including adenoma and adenocarcinoma usually develop in otherwise normal eyes,^{2-4,9,15-18} it occasionally arises from a staphyloma,⁵ juxtapapillary histoplasmosis scar,⁶ CHRPE,^{10,11,19} phthisic eye,^{5,20} chorioretinal scar following a subfoveal neovascular membrane¹⁴ or previous ocular inflammation.³

Acquired RPE tumors are heterogeneous in their clinicopathological appearance. RPE tumors are solitary and unilateral with different sizes. Visual acuity may range between 20/20 to no light perception. Tumors have been

located most often in the peripheral fundus^{4,9,10,16,21} and sometimes at the posterior pole.^{5,14,19} They may occur close to optic disc.^{6,15,17} Although acquired RPE tumors are generally darkly pigmented,^{4,9,15,16} they can also present as an amelanotic pink-red and fleshy masses.^{6,17} Tumors arising from CHRPE can be amelanotic with pigmentation in the deeper part.¹¹ It seems that as these tumors proliferate, some of them lose pigmentation.¹¹ Since RPE tumors occur internal to the Bruch membrane, it is uncommon to observe a classic mushroom or collar-button configuration.¹⁴ The characteristic of acquired RPE tumor is an abruptly elevated mass and sharp borders without hyperpigmentation of surrounding choroidal base.^{3,6} Vitreous seeding has been reported in some cases.^{7,15} Tumors of RPE are more likely to produce vitreous seeding and hemorrhages if the tumor breaks through the sensory retina.^{3,10} One of our patients also developed vitreous hemorrhage without obvious vitreous seeding.

Another distinguishing feature of the acquired RPE tumors is the development of a retinal feeder vessel. Therefore, it is not uncommon for these tumors to exhibit a dilated feeding retinal artery and a drainage retinal vein on fluorescein angiography.^{3,7,18,22} Shields *et al.* found that 8 of 13 (61.5%), RPE tumors had dilated retinal vessels.³ RPE tumors can also produce extensive yellow exudation often leading to

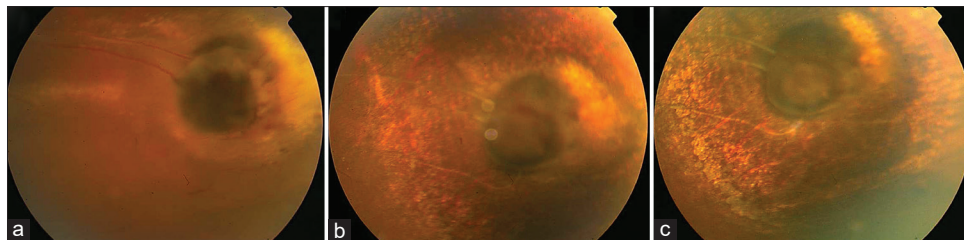


Figure 4: Color fundus photography of Case 2 after 1 month (a), 3 months (b), and 7 months (c) plaque radiotherapy

exudative retinal detachment.^{1,3,16} Preretinal gliosis and cystoid macular edema^{6,11,12} are frequently associated with RPE neoplasia. Retinal and subretinal fibrosis,¹⁴ surface wrinkling retinopathy,¹¹ macular hole, significant ocular inflammation such as uveitis^{9,15,16} or nonspecific choroiditis,^{3,5} secondary cataract,^{7,8,11,18} and secondary glaucoma^{5,8,18} may be found in patients with acquired RPE tumors.³

Ancillary tests may provide some helpful hints in the diagnosis of tumors of the RPE. Transillumination may^{7,11,18} or may not^{6,19} show blockage of light by the tumor. Ocular ultrasonography demonstrates tumors of the RPE to have abruptly elevated dome-shaped mass^{3,6,17} and acoustic solidity^{1,3,6,17} in B-scan as well as high-to-medium internal reflectivity in A-scan.^{1,3,6,8,17} Some cases have been reported as collar button shape,¹⁸ nodular,¹⁹ or mushroom shape,^{1,9} with low to medium internal reflectivity¹⁵ and with choroidal excavation¹⁵ in ultrasonography. Although rare, invasion of the tumor into the adjacent uveal stroma, sensory retina, and vitreous may be seen.³

Angiographic pattern may have a correlation with the structural characteristics of the tumor. Fluorescein angiography reveals some of the gross anatomical features of the tumor, and it is helpful in detecting and defining some of the structural alterations in the tumor tissue.¹⁶ Fluorescein angiography typically shows early hypofluorescence of the tumor during the filling phases, with continued relative hypofluorescence with multiple hyperfluorescent zones and spots,^{9,15,19} and sometimes, leakage into the vitreous^{3,11} in the late frames. Early and late hyperfluorescence areas are due to the window defects and late staining related to sparsely pigmented cells in a more abundant stroma.¹⁶ However, there are some reports that describe the tumor as early and late hyperfluorescent in fluorescein angiography.^{6,11,16} Fluorescein angiography may sometimes demonstrate the retinal blood supply^{14,16} and lack of prominent choroidal vessels (double circulation) or extensive internal vascularity that typify some melanomas.³ Only the second case of our series had obvious feeder vessels in fluorescein angiography, and the other did not show specific pictures.

Indocyanine green angiography reveals intratumoral hyperfluorescence and the presence of intratumoral feeder vessels without associated choroidal vessel dilation that seems to anastomose with retinal vessels.^{8,14,19} Enhanced-depth imaging-OCT shows the tumor surface as irregular or “rugged” with full-thickness retinal tumor and dense posterior optical shadowing.²³

No consensus exists in the management modalities of acquired RPE tumors. There are many reasons for this following dilemma: (1) RPE tumors are very rare and (2) RPE tumors are generally considered to be benign lesions with no tendency to metastasize despite their aggressive nature. Therefore, they can grow and cause profound visual loss.^{3,8,18} When the tumor is small and asymptomatic, periodic observation with fundus photography is reasonable unless progressive or symptomatic lesions such as lipid exudates begin to develop.^{3,5,6}

While enucleation has been the most commonly used treatment because of poor vision, significant local inflammation, pain, or suspicion of melanoma,^{4,6} other treatment modalities have also been tried to avoid globe loss as much as possible. For lesions located in the posterior fundus, the precise role of laser photocoagulation and cryotherapy is not determined, but such modalities could be attempted in patients with early growth or visually threatening complications.^{3,12,13} The efficacy of local resection is also uncertain despite relative success in some peripherally located cases.^{9,10}

The results of radiation therapy in the acquired RPE tumors have not been conclusive till now. Nakamura *et al.*⁸ reported the failure of external-beam radiation to control the symptoms of a patient with RPE adenoma who eventually required enucleation. Shields and Shields mentioned plaque radiotherapy can be used for medium-sized or larger tumors of RPE adenoma in eyes with good vision.²⁴ They observed decreased tumor size without improvement in the visual acuity after iodine-25 plaque brachytherapy in two tumors of RPE with progressive enlargement, visual loss, and increasing exudation.²⁴ On the other hand, Finger *et al.*²¹ did not achieve acceptable outcomes after palladium-103 plaque radiotherapy in a subject of RPE adenocarcinoma who underwent enucleation within 6 months. However, plaque radiotherapy with ruthenium-106 completely stabilized the progressive complications of acquired RPE tumors (adenoma versus adenocarcinoma) in two patients of this series despite relatively poor outcomes in the visual acuity (first case) that was consistent with Shields and Shields report.²⁴

The systemic prognosis of RPE tumors is excellent. None of the RPE tumors reported so far has been associated with metastasis, except in one atypical case with underlying trisomy 21, showing aggressive intraorbital and intracranial optic nerve invasion and multiple intracerebral metastases.²⁵

Loeffler *et al.* also reported a case of RPE malignancy with suspected extraocular extension.²⁰ Some authors believe that an adenocarcinoma of the RPE with extrascleral extension is capable of metastasis to distant sites.²¹ In contrast to systemic involvement, RPE tumors have variable growth potential and the capacity for locally invasive behavior. Although acquired RPE tumors are usually stable for a long time in their clinical course,^{6,7,18} they tend to exhibit progression and local involvement of the choroid,^{1,10,15,17} sensory retina,^{7,18,22} and rarely, extrascleral extension,²⁰ leading to ocular complications and visual loss with time.

In conclusion, plaque radiotherapy can be tried in cases suspicious to acquired RPE tumors that are diagnosed clinically without definite histopathological specimens, especially with good visual acuity, before thinking about more invasive approaches such as enucleation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Adulkar N, Radhakrishnan S, Vidhya N, Kim U. RPE adenocarcinoma as the presenting sign of bronchogenic carcinoma: Diagnostic dilemma in the management of a case. *Case Rep Ophthalmol Med* 2013;2013:786378.
2. Tso MO, Albert DM. Pathological condition of the retinal pigment epithelium. Neoplasms and nodular non-neoplastic lesions. *Arch Ophthalmol* 1972;88:27-38.
3. Shields JA, Shields CL, Gündüz K, Eagle RC Jr. Neoplasms of the retinal pigment epithelium: The 1998 albert ruedemann, Sr, memorial lecture, Part 2. *Arch Ophthalmol* 1999;117:601-8.
4. Shields JA, Eagle RC Jr., Dutton J, Ehya H, Shields CL. Adenocarcinoma of the retinal pigment epithelium: Clinicopathologic correlation with paradoxical immunohistochemical findings. *JAMA Ophthalmol* 2014;132:1249-52.
5. Edelstein C, Shields CL, Shields JA, Eagle RC Jr. Presumed adenocarcinoma of the retinal pigment epithelium in a blind eye with a staphyloma. *Arch Ophthalmol* 1998;116:525-8.
6. Shields JA, Eagle RC Jr., Barr CC, Shields CL, Jones DE. Adenocarcinoma of retinal pigment epithelium arising from a juxtapapillary histoplasmosis scar. *Arch Ophthalmol* 1994;112:650-3.
7. Heegaard S, Larsen JN, Fledelius HC, Prause JU. Neoplasia versus hyperplasia of the retinal pigment epithelium. A comparison of two cases. *Acta Ophthalmol Scand* 2001;79:626-33.
8. Nakamura S, Hikita N, Yamakawa R, Moriya F, Yano H, Furusato E, *et al.* A clinically challenging diagnosis of adenoma of the retinal pigment epithelium presenting with clinical features of choroidal hemangioma. *Clin Ophthalmol* 2012;6:497-502.
9. Palamar M, Shields CL, Marr BP, Eagle RC Jr., Shields JA. Retinal pigment epithelial tumor in a young Asian female. *Eur J Ophthalmol* 2009;19:487-9.
10. Trichopoulos N, Augsburger JJ, Schneider S. Adenocarcinoma arising from congenital hypertrophy of the retinal pigment epithelium. *Graefes Arch Clin Exp Ophthalmol* 2006;244:125-8.
11. Shields JA, Shields CL, Eagle RC Jr., Singh AD. Adenocarcinoma arising from congenital hypertrophy of retinal pigment epithelium. *Arch Ophthalmol* 2001;119:597-602.
12. Klein KA, Lally DR, Taney LS, Laver NV, Duker JS. Retinal pigment epithelial adenocarcinoma presenting as an amelanotic mass. *Ophthalmic Surg Lasers Imaging Retina* 2015;46:369-72.
13. Shields JA, Eagle RC Jr., Shields CL, Brown GC, Lally SE. Malignant transformation of congenital hypertrophy of the retinal pigment epithelium. *Ophthalmol* 2009;116:2213-6.
14. Sommacal A, Campbell RJ, Helbig H. Adenocarcinoma of the retinal pigment epithelium. *Arch Ophthalmol* 2003;121:1481-3.
15. Gkaragkani E, Schalenbourg A, Zografos L. Adenocarcinoma of the retinal pigment epithelium: Clinicopathological case report. *Acta Ophthalmol* 2011;89:10.
16. Ramahefasolo S, Coscas G, Regenbogen L, Godel V. Adenocarcinoma of retinal pigment epithelium. *Br J Ophthalmol* 1987;71:516-20.
17. Asadi AF, Moradi H, Rajabi MT, Riazi EM. Adenocarcinoma of retinal pigment epithelium clinically diagnosed as malignant melanoma: A case report with unsystematic review of literature. *Iranian J of Ophthalmol* 2007;19:43-7.
18. Fan JT, Robertson DM, Campbell RJ. Clinicopathologic correlation of a case of adenocarcinoma of the retinal pigment epithelium. *Am J Ophthalmol* 1995;119:243-5.
19. Moulin AP, Zografos L, Schalenbourg A. RPE adenocarcinoma arising from a congenital hypertrophy of the RPE (CHRPE) treated with proton therapy. *Klin Monbl Augenheilkd* 2014;231:411-3.
20. Loeffler KU, Kivelä T, Borgmann H, Witschel H. Malignant tumor of the retinal pigment epithelium with extraocular extension in a phthisical eye. *Graefes Arch Clin Exp Ophthalmol* 1996;234 Suppl 1:S70-5.
21. Finger PT, McCormick SA, Davidian M, Walsh JB. Adenocarcinoma of the retinal pigment epithelium: A diagnostic and therapeutic challenge. *Graefes Arch Clin Exp Ophthalmol* 1996;234 Suppl 1:S22-7.
22. Graham GC. Juxtapapillary retinal pigment epithelial tumor. Adenocarcinoma vs. reactive hyperplasia. *Arch Ophthalmol* 1971;85:299-301.
23. Shields CL, Manalac J, Das C, Saktanasate J, Shields JA. Review of spectral domain-enhanced depth imaging optical coherence tomography of tumors of the retina and retinal pigment epithelium in children and adults. *Indian J Ophthalmol* 2015;63:128-32.
24. Shields JA, Shields CL. Tumors and related lesions of the pigmented epithelium. *Asia Pac J Ophthalmol (Phila)* 2017;6:215-23.
25. Heindl LM, Naumann GO, Kruse FE, Holbach LM. Aggressive metastasizing adenocarcinoma of the retinal pigment epithelium with trisomy 21. *Br J Ophthalmol* 2008;92:389-91.