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Update in Ocular Melanoma

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1. Introduction

1.1. Ocular anatomy

In order to understand the pathophysiology of this condition we will describe the *uvea* anatomy.

The Iris is a contractile diaphragm that controls the degree of retinal illumination, it has a central aperture, the pupil, located slightly nasally. It consists of the following layers from anterior to posterior:

1. Stroma: a thin avascular layer with fibroblasts and melanocytes. It is heavily pigmented in persons with brown eyes less pigmented in green and hazel irises and least in blue. Posteriorly, the stroma contains the sphincter pupillae muscle (parasympathetic, miosis).
2. Pigment epithelium: consists of 2 layers of cells: -anterior layer, which intermingles with the dilator pupillae muscle (sympathetic, mydriasis) -posterior layer, which is continuous with the pigment epithelium of the ciliary body and RPE of the retina, all having the same embryologic origin.

The ciliary body is one of the three parts of the uvea and extends for 6 mm from the end of the retina (ora serrata) till the scleral spur. Its epithelial portion (adjacent to vitreous) consists of a posterior portion (pars plana) and an anterior portion (pars plicata). The latter has 60-70 folds called the ciliary processes which secrete the aqueous humor into the posterior chamber. Its uveal portion contains the ciliary muscle which has 3 parts, all under parasympathetic innervation: longitudinal (outermost), radial and circular.

The choroid is a dark brown vascular sheet, 0.25mm thick, lying between the sclera and the retina. The outer vascular bed has large vessels (layer of Haller) and the inner bed consists of an extensive network of fenestrated vessels, the choriocapillaris which is the major blood supply to the outer layers of the retina and to the whole macula. The inner layers, up to the middle of the Pigmented Epithelium are supplied by the central retinal artery.

1.2. Difference between ocular melanoma and cutaneous melanoma

Ocular and cutaneous melanomas show several differences despite they both derive from melanocytes. Both malignancies show a high tendency to metastasize though they display different preferential sites. Skin melanomas spread to distant skin sites, lung, liver, central nervous system and bone. However uveal melanoma, the most frequently diagnosed of the ocular melanomas, gives rise to metastases almost exclusively in the liver which is affected in 90% of the cases.

Interestingly, both malignancies display similar chromosomal aberrations as well as a similar gene expression profile [1]. The similarity in this aspect, despite the difference in tumor behaviour, serves as a proof of the role of the microenvironment in tumor development.

With respect to the early diagnosis, in the skin melanoma the suspected diagnosis and the subsequent clinical follow-up are based on the ABCDE rule. On the other hand, in the diagnosis of ocular melanoma the most relevant information comes from the ophthalmoscopy and the ultrasonography. Finally, consulting times for patients and prognosis are different for both types of melanoma.

2. Objectives

In this chapter we will focus in the clinical management of ocular melanoma from the diagnosis to the treatment.

3. Immunopathology

The eye is an immunologically privileged site; from an evolutionary point of view this condition helps to control or eliminate pathogens while generating the least inflammatory damage to the ocular tissues. However, the counterpart of this phenomenon is that it favors the escape of the tumor cells from the controls of the immune system, facilitating the growth of the uveal melanoma and its metastatic dissemination. Experiments in mice have shown that cytotoxic cell activity in the ocular tissue might be modulated by two mechanisms:

1. By direct interference of the specific effector function of CD8 + lymphocytes.
2. Indirectly affected by stimulation of macrophages [2].

The inhibition of macrophage action was expressed by an insufficient production of nitric oxide in the ocular tissue, which is known to modulate the tumoricidal activity of cytotoxic T lymphocytes [3]. It has also been shown that tumor rejection in mice by the CD8 + CTL is mediated by TNF- α [4].

The study of the mechanisms that facilitate the growth of an immunogenic tumor in the anterior chamber, demonstrated an influx of CD8 + CTL infiltrating the tumor. This phenomenon was preceded by intratumoral accumulation of CD11 + myeloid cells B, which exert a powerful immunosuppressive activity on the CTL, facilitating tumor escape from the immune system. Regulatory T cells, myeloid suppressor cells and stroma cells could also reduce the delayed type hypersensitivity reaction to induce apoptosis of CD8 + and NK cells [5]

4. Demographic and epidemiological data

The *racial* background of the patient is an important factor. Whites have been shown to be eight times more likely to develop choroidal melanoma than African-Americans. This trend is also observed in skin melanoma, whites are six times. More likely to develop this malignancy than African-Americans [6-7]. The individuals with light iris are at increased risk of developing uveal melanoma. This is a finding that implicates *sunlight exposure* as an important environmental risk factor. The protective effect of melanin may be particularly important in the iris as it is the only part of the uveal tract positioned in front of the lens, which serves as an effective ultraviolet filter.

The median *age* at diagnosis is about 55-65 years and the incidence decreases after 70 years of age. With regards to incidence depending on *sex*, there is a slight predominance of males [8].

In a study involving 4500 patients with uveal melanoma, only 0.6% of the cases had a family history of this disease [9]. Thus *heredity* does not seem to be a significant determinant of uveal melanoma. With respect to *occupational and chemical exposures*, the only specific occupational exposure that has been linked to uveal melanoma is welding. Ocular melanomas have been induced in laboratory animals after administration of *radium, methylcholanthrene, N-2fluorenylacetamide, ethionine and nickel subsulfide*.

5. Diagnosis of ocular melanoma

Accuracy in the early diagnosis of ocular melanoma is crucial to improve the prognosis. Currently the diagnosis of ocular melanoma is based on both the clinical experience of the specialists and on the use of modern diagnostic techniques.

The rate of misdiagnosis for eyes enucleated for choroidal melanoma was 20 % until the 1970's but it has decreased to 1% since then. [10-16]

5.1. Clinical

The most common symptoms include *visual loss, photopsias and visual field defects*. None of these symptoms are specific of choroidal melanoma. Pain is very atypical in ocular melanoma, except in those cases that present massive extraocular extension, inflammation or neovascular glaucoma.

Indirect Ophthalmoscopy through a well-dilated pupil is the most important examination in the diagnosis of choroidal melanoma. The classic image is a pigmented, dome-shaped or collar button-shaped tumor in a minority of cases and an associated exudative retinal detachment, orange tumor pigmentation (Lipofuscin) and sentinel vessels (prominent episcleral vessels especially in those involving ciliary body). Scleral transillumination has been advocated by Reese. [17]

The lesions most commonly mistaken for choroidal melanoma are choroidal nevus (49%), peripheral exudative hemorrhagic chorioretinopathy (8%), congenital hypertrophy of the retinal pigment epithelium (6%), hemorrhagic detachment of the retina or pigment epithelium (5%), circumscribed choroidal hemangioma (8%) and age related macular degeneration (4%) [18]

5.2. Complementary studies

Ultrasonography: The most important ancillary test in the evaluation of a patient with intraocular mass lesions is the combination of both A-mode and B-mode ultrasonography (see Box 1). For tumors larger than 3 mm in thickness, a combination of both scans in skilled hands can diagnose choroidal melanomas with greater than 95% accuracy [19].

A-mode:

1. *medium to low internal echoes with smooth attenuation.*
2. *vascular pulsations within the tumor*

B-mode: 3 classic features

1. *Low to medium reflectivity within the melanoma.*
 2. *Choroidal excavation.*
 3. *Shadowing in the orbit.*
-

Box 1. Ultrasonography

Fluorescein angiography: Early hyperfluorescence with late leakage and multifocal punctate hyperfluorescence. This study is of major importance in order to distinguish lesions that simulate choroidal melanoma.

Other studies like Optical Coherence Tomography and Indocyanine Green angiography may be useful in the diagnosis of this pathology. Magnetic resonance imaging, nuclear magnetic resonance spectography, color Doppler ultrasonography, electrophysiologic testing and immunologic testing do not offer reliable results. [20-26]

6. Current medical management of patients with Ocular Melanoma

a. Cytogenetic: Personalized Targeted Therapy

Currently much effort is directed toward understanding uveal melanoma genetics and genomics [27], hoping that this knowledge will contribute to the development of effective molecular therapies

Inhibitors of B.Raf and MEK kinases hold promise for treatment of cutaneous melanomas harboring BRAF mutations. BRAF are rare in ocular melanomas, but somatic mutations in the G protein alpha subunits G alpha q and G alpha 11 (encoded by *Gnaq* and *Gna11*, respectively) occur, in a mutually exclusive pattern, in 80% of uveal melanomas. The impact of the B-Raf inhibitor PLX4720 and the MEK inhibitor AZD6244, the AKT inhibitor MK2206 and the PKC inhibitors bisindolylmaleimide I (GF109203X) has been assessed [28].

A randomized phase II study compared MEK inhibition (AZD6244) to temozomide in advanced uveal melanoma. MEK inhibition seems to be a rationale therapeutic strategy in uveal melanoma, using *Gnaq/11* as a potential predictor of sensitivity [29].

b. Surgery: Resection/Enucleation

Enucleation is indicated when the tumor size exceeds 16 mm of base and 10 mm of height, is diffuse and with bad prognosis; however it is very important to emphasize that there is no scientific evidence of increased survival after enucleation. Also, enucleation does not prevent metastases.

A novel minimally invasive surgical technique for resection of selected cases of small iris tumours has been described. This technique avoids the potential morbidity associated with a large corneoscleral incision allowing for rapid visual recovery [30].

Radiotherapy, *Brachytherapy* (BT: I125, 103 Pd, 131 Cs, Ru) and Proton Beam Radiotherapy (PBRT)

The most commonly employed form of radiotherapy has been the application of an episcleral radioactive plaque and the most frequently employed isotopes include ⁶⁰Co (*Cobalt*), ¹⁰⁶Ru (*Ruthenium*), ¹⁹²Ir (*Iridium*) and ¹²⁵I (*Iodine*) [31-32].

It is extremely important to highlight the conservative treatment of melanoma, proposed by *Irarrazabal A. et al* using brachytherapy. This procedure has shown positive results in preserving the eye, without increase in mortality. Moreover useful vision was retained in more than half of the treated patients [33].

In a study comparing patients treated with *Ruthenium* brachytherapy with patients undergoing simultaneous thermotherapy or BT alone, combined treatment provided higher local control, eye globes preservation, better recurrence-free survival rates, lower rates of metastases and prolonged survival than treatment with BT alone.

I125 episcleral brachytherapy in uveal melanoma is effective in tumor control, allowing preservation of the eye and useful visual function for the majority of patients [34].

It has been suggested that length of remaining life after diagnosis of uveal melanoma is similar following enucleation (removal of the eye) to local eye-conserving radiotherapy. The multidisciplinary COMS Group emphasized that there were no differences in survival outcomes and a small difference in quality-of-life outcomes between patients in the brachytherapy arm and those in the enucleation arm [35].

Radiation treatment was found to reduce the tumor in 94% of the cases. Mean tumor thickness decreased from 3.7 to 2.5 and 2.1 after 3 and 5 years respectively. Recurrence occurred in 6% of the treated patients. Although this therapy is associated with complications like radiation optic neuropathy in 81% and vitreous bleeding in 30% of cases, it is a promising treatment given that enucleation was necessary in only 3% of patients and metastasis developed in 15% during follow up. Even though the visual acuity decreases considerably after optic disc irradiation with proton beam therapy, the rates of tumor control and eye retention are favourable.

The second most frequent method of radiotherapy is the use of heavy ions such as *Proton Beam Radiotherapy* [36]. In a comparison of the efficacy of PBRT and Ruthenium-106 notched plaque radiotherapy with or without TTT for the treatment of juxtapapillary choroidal melanoma, it was found that the tumors were successfully treated using either proton beam or notched plaque combined with adjuvant TTT [37]. However, vision is often sacrificed. On the other hand, Notched plaque alone is not as efficient in reducing the tumor but results in improved visual outcome [37].

Proton beam irradiation of uveal melanoma has great advantages over brachytherapy because of the homogenous dose delivered to the tumor and the possibility of sparing normal tissue close to the tumor. Complications such as retinal detachment, maculopathy, papillopathy, cataract, glaucoma, vitreous hemorrhage and dryness are described. The severest complication that usually leads to secondary enucleation is neovascular glaucoma and it is encountered after irradiation of large to extra-large tumors. It is hypothesized that the residual tumor scar may produce proinflammatory cytokines and Vascular endothelial growth factor- VEGF (toxic tumor syndrome) leading to intraocular inflammation and neovascular glaucoma. Additional treatments after proton beam such as transpupillary thermotherapy, endoresection of the tumor scar or intravitreal injections of anti-VEGF may reduce the rate of these complications [38].

c. Monoclonal Antibodies

Current systemic treatments for metastatic uveal melanoma have not improved overall survival. The fully human anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal anti-

body, *ipilimumab*, improved overall survival of patients with advanced cutaneous melanoma in a phase 3 trial. However, uveal melanoma patients were excluded from this study. A sub-analysis, performed by the ipilimumab-ocular melanoma expanded access program (I-OMEAP) study group, aimed at assessing the activity and safety of ipilimumab in patients with uveal melanoma in a setting similar to daily clinical practice. The results indicated that uveal melanoma is a potential target for ipilimumab treatment and that it should be further investigated in clinical trials [39].

The *R24 monoclonal antibody*, that recognizes the disialoganglioside GD3 expressed on the surface of malignant melanoma cells, could mediate destruction of these cells. A combination of R24 with a low dose of IL-2 was found to promote destruction of cultured melanoma cells and it can be safely administered to patients with metastatic melanoma [40].

d. Transpupillary Thermotherapy (TTT):

Choroidal melanomas should be diagnosed and treated at the very early stage as the initial spread of metastases is thought to occur during the proliferative stage of tumor development.

TTT is recommended for the management of posterior choroidal nevi suspected for malignant transformation or small choroidal melanomas that are less than 2-5 mm in thickness [41]. TTT might be the treatment of choice for selected, very small melanomas. However, studies with long follow-up and large number of patients are needed to evaluate its effectiveness.

Choroidal melanomas treated with TTT as stand-alone procedure need a close monitoring since these tumors developed a significant rate of local recurrences and ocular side-effects in the long run.

e. Antiangiogenic drugs (Bevacizumab)

Anti-angiogenic therapy is based on the assumption that a tumor cannot grow beyond the limits of diffusion (about 1-2 mm) of oxygen and nutrients from capillaries, unless angiogenesis takes place. VEGF plays a key role in angiogenesis, regulating vasopermeability and the proliferation and migration of endothelial cells. VEGF levels are significantly elevated in uveal melanoma patients with metastatic disease compared to patients without metastases. Anti-angiogenic therapy, such as bevacizumab, is currently used for the treatment of metastases of several malignancies. [43].

Bevacizumab may be used as an adjuvant agent when used following plaque brachytherapy in the treatment of choroidal melanoma. The combination of this treatments was assessed in an interventional case series of 100 patients treated from 2006-2008 for choroidal melanoma and the results were satisfactory. Melanoma specific mortality was 0% at 9 months after treatment. Mean visual acuity for combined treatment at 6 months was 20/30 [42]

The *bevacizumab - radiotherapy combination* could be a promising clinical approach for the management of human uveal melanoma, since it may allow the use of lower doses of radiotherapy without compromising the antitumor effect [44].

f. Chemotherapy

There is no current evidence that chemotherapy has a significant role in the primary management of uveal melanoma. Such treatment may prolong survival for a few months but it is unlikely that it will be curative.

Uveal melanoma metastases develop in 6.5-35% of patients, most commonly to the liver. Metastatic uveal melanoma survival is poor, with 5-7 months of median survival. A retrospective study including 58 patients with uveal melanoma metastases showed that the median overall survival (OS) for all the patients was 10.83 months. Patients who had undergone chemotherapy presented 10.83 months of median OS whereas the patients who did not undergo this treatment had an OS of 8.033 months. Patients with metastatic uveal melanoma should be included in clinical trials evaluating other options with newer agents [45].

g. Others (Adjuvant therapy with interferon, Imatinilo Mesylate, Paclitaxeldocosahexaenoic Acid, Factionated Radiosurgery Cyberknife, aflibercept, vaccine).

7. Medical prognosis: Mortality (Hepatic metastasis), loss of the eye, loss of vision

These three variables will affect directly the patient survival:

Variable	Importance for prognosis
A Size (Base more than 16 mm and altura more than 10 mm).	+
B Cell Type (Epitheloid Cells)	++
C Genetic Type (GEP: Gene Expression Profile)	+++

Prognosis: GEP (Gene Expression Profile) In a prospective evaluation involving 514 uveal melanoma patients [46], the gene expression profile prognostic assay helped in classifying the primary tumor into two prognostic subgroups:

Class I (60% of the cases)

Low metastatic risk :

IA (87%) almost without metastasis (0.8% of the patients).

IB (13%) few metastasis (10.8%) + disomy cr3 few metastasis.

Class II (40% of the cases)

High metastatic risk: metastasis (29.8%) + monosomy or pseudodisomy cr3 metastasis is not sure, + Trisomy cr6: 80 % of patients will show metastasis 4 years after diagnosis.

This classification might be helpful for the prognosis in three aspects: in the screening targeted to metastasis, in the earlier diagnosis of the metastasis and for an earlier preventing treatment of the metastasis in high risk cases. In this regard, it is important to highlight that there is no scientific evidence about increased survival due to metastasis treatment [47].

8. Uveal melanoma TNM staging and survival: Implications in patient management and prognosis

Damato, B; Eleuteri, A [48] support the idea that Kaplan-Meier survival curves based only in tumour size and extend do not provide a true indication of prognosis. This is because the survival prognosis in uveal melanoma correlates not only with clinical stage but also with histologic grade, genetic type and competing causes of death. They propose an online predictor tool using the following data:

8.1. Parameters

Age

Sex

Large ultrasound diameter

Ciliary body involvement

Extraocular extension

Years since treatment

Epithelloid Cells

Closed PAS+ ve loops

Mitotic rate/40

Monosomy 3

Regional Lymph nodes

Distant metastasis

First scan (years)

Threshold for next scan (number)

8.2. TNM Stage

C.

Survival

Controls

Subjects

Difference

Relative

9. Conclusion

The uveal melanoma, which arises from melanocytes residing in the stroma, is the most common primary intraocular tumour in adults. More than 90% involve the choroid, the remainder being confined to the ciliary body and iris.

The most common symptoms in uveal melanoma include visual loss, photopsias and visual field defects but none of these symptoms are specific of this malignancy. Diagnosis is based on slit-lamp biomicroscopy and/or ophthalmoscopy, with ultrasonography, autofluorescence photography. Although each day we count with more variety and helpful complementary studies, suspicious lesions should be closely monitored. Uveal melanomas are diverse in their clinical features and behaviour. Despite ocular treatment almost 50% of patients with primary uveal melanoma will develop distance metastasis [50]. The metastatic disease occurs almost exclusively in patients whose tumour show chromosome 3 loss and/or class 2 gene expression profile. When the tumour shows such lethal genetic changes, the survival time depends on the anatomical stage and the histological grade of the malignancy.

Prognostication has improved as a result of progress in multivariate analysis including all the major risk factors.

Screening for metastases is more sensitive as a consequence of the advances in liver scanning with magnetic resonance imaging and other methods. More patients with metastases are living longer, benefiting from therapies such as: partial hepatectomy; radiofrequency ablation; ipilimumab immunotherapy; selective internal radiotherapy; intra-hepatic chemotherapy, possibly with isolated liver perfusion; and systemic chemotherapy [48].

Conservation of the eye with useful vision has improved thanks to the advances in brachytherapy, proton beam radiotherapy, transpupillary thermotherapy. The current trend is to try to preserve the affected eye by all means, as there is no scientific evidence that shows that removing the affected eye will improve survival.. This is a great difference in the treatment of ocular vs cutaneous melanoma. The specialists must take into consideration the need to protect the eye with melanoma and preserve as much vision as possible as the other eye may be affected by another pathology in the future with the consequent loss of vision.

On the basis of the currently available information it appears that patients treated with radiotherapy have a survival rate at least as good, if not better than those treated with enucleation [36].

Several drugs, such as bortezomib, celecoxib, dacarbazine, anti-angiogenic agents (such as bevacizumab, sorafenib and sunitinib), temsirolimus, mitogen-activated protein kinase kin-

ase (MEK) inhibitors, ipilimumab and AEB071 are candidate drugs, and studies are underway to determine the therapeutic effects of these drugs in uveal melanoma [51].

Currently, the aim is to improve the detection of uveal melanoma so as to maximize the opportunities for conserving the eye and vision, as well as preventing metastatic spread. Patient management has been enhanced by the formation of multidisciplinary teams in specialized ocular oncology centers all over the world.

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References

- [1] Van den Bosch T, Kilic E, Paridaens D, de Klein A. Genetics of uveal melanoma and cutaneous melanoma: two of a kind? *Dermatol Res Pract*. 2010;2010:360136.
- [2] Vicetti Miguel RD, Cherpes TL, Watson LJ, Mc Kenna KC: CTL induction of tumoricidal nitric oxide production by intratumoral macrophages is critical for tumor elimination. *J Immunol* 2010, 185:6706-18.
- [3] Dace DS, Chen PW, Niederkorn JY: CD8+ Tcells circumvent privilege in the eye and mediate intraocular tumor rejection by aTNF-alfa dependent mechanism. *J Immunol*, 2007, 178:6115-22
- [4] McKenna KC, Kapp JA: Accumulation of immunosuppressive CD11B+ myeloid cells correlates with the failure to prevent tumor growth in the anterior chamber of the eye. *J Immunol*, 2006, 177:1599-608.
- [5] Poggi A, Zocchi MR: Mechanisms of tumor escape: role of tumor microenvironment inducing apoptosis of cytolytic effector cells. *Arch. Immunol The Exp (Warsz)* 2006, 54:323-33.

- [6] Margo CE, Mc Lean IW: Malignant melanoma of the choroid and ciliary body in black patients. *Arch Ophthalmol* 1984; 102:77-79.
- [7] Graham BJ, Duane TD: Meetings, conferences, symposia: report of ocular melanoma task force. *Am J Ophthalmol* 1981; 90:728-733.
- [8] Gragoudas ES: First 1000 patients with uveal melanoma treated by proton beam irradiation. Presented at the second International Meeting in the Diagnosis and Treatment of Intraocular Tumors in Nyon, Switzerland, November, 1987.
- [9] Singh AD, Shields CL, De Potter P, Shields JA, Trock B, Cater J, Pastore D. Familial uveal melanoma. Clinical observations on 56 patients. *Arch Ophthalmol*.1996 Apr; 114(4):392-9.
- [10] Ferry AP: Lesions mistaken for malignant melanoma of the posterior uvea: a clinico-pathologic analysis of 100 cases with ophthalmoscopically visible lesions. *Arch, Ophthalmol* 1964; 72:463-469.
- [11] Shields JA, Zimmerman LE: Lesions simulating malignant melanoma of the posterior uvea. *Arch Ophthalmol* 1973; 89:466-471.
- [12] Zimmerman LE: Bedell Lecture. Problems in the diagnosis of malignant melanoma of the choroid and ciliary body. *Am J Phthlalmol* 1973; 75:917-929.
- [13] Chang M, Zimmerman LE. Mc Lean IW: The persisting pseudomelanoma problem. *Arch Ophthalmol* 1984, 102:726-727.
- [14] Shields JA, Augsburger JJ, Brown GC, Stephens RF: The Differential diagnosis of posterior uveal melanoma. *Ophthalmology* 1980; 87:518-522.
- [15] Shields JA, Mashayekhi A, Ra S, Shields CL: Pseudomelanomas of the posterior uveal tract. *Retina* 2005; 25:767-771.
- [16] Char DH, Stone RD, Irvine AR, et al: Diagnostic modalities in choroidal melanoma. *Am J Ophthalmol* 1980; 89:223-230.
- [17] Reese AB: Tumors of the eye 3rd edn. Hagerstown, MD: Harper & Row; 1976:174-262.
- [18] Shields JA, Mashayekhi A, Ra S, Shields CL: Pseudomelanomas of the posterior uveal tract. *Retina* 2005; 25:767-771
- [19] Char DH, Stone RD, Irvine AR, et al: Diagnostic modalities in choroidal melanoma. *Am J Ophthalmol* 1980; 89:223-230.
- [20] Char DH: Inhibition of leukocyte migration with melanoma-associated antigens in choroidal tumors. *Invest Ophthalmol Vis Sci* 1977; 16:176-179.
- [21] Brownstein S, Phillips TM, Lewis MG: Specificity of tumor-associated antibodies in serum of patients with uveal melanoma. *Can J Ophthalmol* 1978; 13:190-193.
- [22] Felberg NT, Donoso LA, Federman JL: Tumor-associated antibodies in the serum of patients with ocular melanoma. *Ophthalmology* 1980; 87:529-533.

- [23] Felberg NT, Pro-Landazuri JM, Shields JA, Federman JL: Tumor-associated antibodies in the serum of patients with ocular melanoma. *Arch Ophthalmol* 1979; 97:256-259.
- [24] Donoso LA, Felberg NT, Edelberg K, et al: Metastatic uveal melanoma: an ocular melanoma-associated antigen in the serum of patients with metastatic disease.
- [25] Meyer F, Naron d, Zonix S: The role of carcinoembryonic antigen in surveillance of patients with choroidal melanoma: a prospective study. *Ann Ophthalmol* 1987; 19:24-25.
- [26] Bomanji J, Hungerford JL, Granowska M, Britton Ke: Radioimmunoscintigraphy of ocular melanoma with 99m Tc labeled cutaneous melanoma antibody fragments. *Br J Ophthalmol* 1987; 71:651-658.
- [27] Leyvraz S, Keilholz U: Ocular Melanoma: what's new? *Curr Opin Oncol*. 2012 Mar; 24(2):162-9.
- [28] Vasiliki Poulaki, Sue Anne Chew, Bin He, Nicholas Mitsiades. Personalized Targeted Therapy harboring GNAQ and GNA 11 Mutations. Inhibition of genes (Mek, B-Raf, Akt, PkC). Uveal Melanoma. XVth Biannual Meeting ISOO International Society of Ocular Oncology, 2011, Nov 14-17.
- [29] Carvajal R, Wolchok JD, Chapman PB, Dickson M, Bluth M, Ambrosini G, Marr B, Heinemann M, Fusco A, Nalysnyk, Martin N, Doyle A, Bastian B, Abramson D, Schwartz G: Rationale, study design and accrual status of a randomized phase II study of AZD6244, a MEK inhibitor, vs temozomide in advanced uveal melanoma. XVth Biannual Meeting ISOO International Society of Ocular Oncology, 2011, Nov 14-17.
- [30] Singh A: Resection of iris tumours: Internal approach. XVth Biannual Meeting ISOO International Society of Ocular Oncology, 2011, Nov 14-17.
- [31] Shields JA, Augsburger JJ, Brady LW, Day JL: Cobalt plaque therapy of posterior uveal melanomas. *Ophthalmology* 99:1201-1207, 1982.
- [32] Shields JA: *Diagnosis and Management of Intraocular Tumours*. St. Louis, the CV Mosby Co, 1983.
- [33] Irrarrázabal A, Cazon P: Results of melanoma brachytherapy in Argentina. XVth Biannual Meeting ISOO (International Society of Ocular Oncology), 2011, Nov 14-17.
- [34] García-Álvarez C, Saornil MA, López-Lara F, Almaraz A, Muñoz MF, Frutos-Baraja J, Muiños Y: Episcleral brachytherapy for uveal melanoma: analysis of 136 cases. *Clin Transl Oncol*. 2012 May;14(5):350-5.
- [35] Hawkins BS: Collaborative ocular melanoma study randomized trial of I-125 brachytherapy. *Clin Trials*. 2011 Oct;8(5):661-73.

- [36] Gragoudas ES, Goiten M, Verhey L, Munzenreider J, Suit HD, Kohler A: Proton Beam irradiation, an alternative to Enucleation for intraocular melanoma. *Ophthalmology* 87:571-581, 1980.
- [37] Tsimpida M, Hungerford J, Cohen V: Treatment of juxtapapillary choroidal melanoma. XVth Biannual Meeting ISOO International Society of Ocular Oncology, 2011, Nov 14-17.
- [38] Damato B: Progress in the management of patients with uveal melanoma. *Eye (Lond)*. 2012 Jun 29. The 2012 Ashton Lecture. [Epub ahead of print]
- [39] Danielli R, Ridolfi R, Chiarion-Sileni V, Queirolo P, Testori A, Plummer R, Boitano M, Calabró L, Rossi CD, Giacomo AM, Ferrucci Pf, Ridolfi L, Altomonte M, Miracco C, Balestrazzi A, Maio M: Ipilimumab in pretreated patients with metastatic uveal melanoma.: safety and clinical efficacy. *Cancer Immunol Immunother*, 2012 Jan; 61(!): 41-8. Epub 2011 Aug 11.
- [40] Soiffer RJ, Chapman PB, Murray C, Williams L, Unger P, Collins H, Houghton AN, Ritz J: Administration of R24 monoclonal antibody and low-dose interleukin 2 for malignant melanoma. *Clin Cancer Res*, 1997 Jan; 3(1):17-24.
- [41] Mordechai R, Moroz I, Moisseiev J, Vishnevskia-Dai V: Our experience with transpupillary thermo therapy for suspected or small choroidal melanomas. XVth Biannual Meeting ISOO International Society of Ocular Oncology, 2011, Nov 14-17.
- [42] Houston SK, Murray T, Markoe A, Pina Y, Decatur C: Intravitreal bevacizumab as an adjuvant agent when used immediately after treatment with plaque brachytherapy. XVth Biannual Meeting ISOO International Society of Ocular Oncology, 2011, Nov 14-17.
- [43] el Filali M, van der Velden PA, Luyten GP, Jager MJ: Anti-angiogenic therapy in uveal melanoma. *Dev Ophthalmol*. 2012;49:117-36. Epub 2011 Oct 21.
- [44] Sudaka A, Susini A, Lo Nigro C, Fischel JL, Toussan N, Formento P, Tonissi F, Lattanzio L, Russi E, Etienne-Grimaldi MC, Merlano M, Milano G: Combination of bevacizumab and irradiation on uveal melanoma: an in vitro and in vivo preclinical study. *Invest New Drugs*. 2012 Jun 20. [Epub ahead of print]
- [45] Pons F, Plana M, Caminal JM, Pera J, Fernandes I, Perez J, Garcia-Del-Muro X, Marcoval J, Penin R, Fabra A, Piulats JM: Metastatic uveal melanoma: is there a role for conventional chemotherapy? - A single center study based on 58 patients. *Melanoma Res*. 2011 Jun;21(3):217-22.
- [46] Harbour JW, Onken M, Worley L, Augsburger J, Correa Z, Devron HC, Nudleman E, Aaberg TJr, Altaweel MM, Bardenstein D, Finger P, Gallie B, Harocopos GJ, Hovland PG, McGowan H, Milman T, Mruthyunjaya P, Simpson ER, Smith M, Wilson D, Wirnstko WJ: Prospective evaluation of a gene expression profile prognostic assay for uveal melanoma in 514 patients. XVth Biannual Meeting ISOO International Society of Ocular Oncology, 2011, Nov 14-17.

- [47] Augsburger JJ, Correa ZM, Shaikh AH: Quality of evidence about effectiveness of treatments for metastatic uveal melanoma, *Trans Am Ophthalmol Soc*, 2008; 106:128-35; discussion 135-7.
- [48] Damato B, Eleuteri A, Taktak AF, Coupland SE: Estimating prognosis for survival after treatment of choroidal melanoma. *Prog Retin Eye Res*, 2011 Sep; 30(5):285-95. Epub 2011 May 30.
- [49] *Eye (Lond)*. 2012 Jun 29. doi: 10.1038/eye.2012.126. [Epub ahead of print]
- [50] Spagnolo F, Caltabiano G, Queirolo P: Uveal Melanoma. *Cancer Treat Rev* 2012 Aug; 38(5):549-53. Epub 2012 Jan 24.
- [51] Velho TR, Kapiteijn E, Jager MJ: New therapeutic agents in uveal melanoma. *Anti-cancer Res*. 2012 Jul;32(7):2591-8.

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