

## Diagnosis and Management of Uveal Melanoma

Anna E Koopmans,<sup>1</sup> Annelies de Klein,<sup>2</sup> Nicole C Naus<sup>3</sup> and Emine Kilic<sup>3</sup> (for the Rotterdam Ocular Melanoma Study Group)

1. Medical Doctor, Department of Clinical Genetics and Ophthalmology; 2. Associate Professor, Department of Clinical Genetics;

3. Ophthalmologist, Department of Ocular Oncology, Erasmus Medical University Centre, Rotterdam, the Netherlands

### Abstract

Uveal melanoma (UM) is the most common cause of primary eye cancer in the developed world. UM may arise in the iris, ciliary body or choroid. Choroidal melanomas are the most frequent and usually display a discoid, dome- or mushroom-shaped growth pattern. Diagnosis is based on a clinical examination with the slit lamp and indirect ophthalmoscope together with ultrasonography of the eye. Despite improvements of primary treatment and a shift towards more conservative eye treatments, survival has not improved during the past decades. Aims of conservative treatment of UM are to elucidate the tumour and to retain the eye and in some cases the visual function. Primary treatment of UM consists of several options such as brachytherapy with either ruthenium-106 (Ru-106) and iodine-125 (I-125) isotopes, transpupillary therapy, proton beam therapy, stereotactic radiotherapy, photodynamic therapy and surgical excision. Enucleation must be reserved for patients with large or advanced tumours, or when extraocular extension is present.

### Keywords

Uveal melanoma, ocular tumour, diagnosis, management, therapy, metastases

**Disclosure:** The authors have no conflict of interest to declare.

**Received:** 14 January 2013 **Accepted:** 30 March 2013 **Citation:** *European Ophthalmic Review*, 2013;7(1):56–60 DOI: 10.17925/EOR.2013.07.01.56

**Contact:** AE Koopmans, Erasmus University Medical Centre, Department of Ophthalmology, room number Ee-1610, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands.

E: a.koopmans@erasmusmc.nl

Uveal melanoma (UM) is the most common primary intra-ocular malignancy in adults. The incidence of UM ranges from 4.3 to 10.9 cases per million and has remained stable for the past 50 years.<sup>1</sup> Presentation is at a median age of 60 years, and men and women are equally affected. UM is a neoplasm that arises from melanocytes in the uveal tract, which comprises the choroid, ciliary body and iris. Choroidal melanomas are the most common and display a discoid, dome-shaped or mushroom-shaped growth pattern. UM have a strong tendency to metastasise to the liver. Over the past decades, ocular ophthalmologists have shifted towards more eye-conserving treatment with the aim of preserving vision. Despite primary treatment, nearly half of the patients eventually die due to metastatic disease and the patient survival has not improved over the past 30 years.<sup>2</sup> Metastasising UMs often contain non-random chromosomal aberrations, such as loss of chromosome 3 and gain of chromosome 8q. Research focuses on finding genetic prognostic markers in UM to select those patients at risk of developing metastatic disease. The most recent results are the tumour-specific mutations that have been found in *GNAQ*, *GNA11* and *BAP1* genes.<sup>3–5</sup> These latest findings can have implications for the future therapy of UM by developing new treatments based on the specific gene content. In this article we will review the diagnosis and current treatment modalities for choroidal melanomas as well as metastases. The future prospects regarding therapeutic options will also be discussed.

### Clinical Diagnosis

UM are often noticed at a routine ophthalmic examination since 30 % of the patients have no symptoms.<sup>6</sup> If a patient with UM presents

with symptoms, these can include blurred vision, floaters, photopsias and visual loss, depending on the size and location of the tumour. In some cases the patient presents with severe ocular pain secondary to inflammation or neovascular glaucoma.

The diagnosis of UM is based on clinical examination with the slit lamp and indirect ophthalmoscope together with ultrasonography (US) of the eye. The majority of UM are pigmented lesions (melanotic), only one-quarter is amelanotic or relatively non-pigmented. The tumours can grow towards the vitreous displaying a discoid, dome-shaped or mushroom-shaped growth pattern. Small melanomas are more difficult to detect than medium- and large-sized melanomas. UM are subdivided according to the apical size of the tumour and the diameter. Small melanomas have a diameter of >5 mm with a thickness of 1.0 to 2.5 mm, medium-sized lesions are <16 mm in diameter and 2.5 to 10.0 mm thick and large UM are either >16 mm in diameter with a thickness of >2.0 mm or have a thickness of >10.0 mm regardless of the basal diameter.<sup>7</sup> They can appear flat or dome-shaped. It remains challenging for ophthalmologists to differentiate between small choroidal melanomas and choroidal nevi, and the latter are the most important differential diagnosis of UM. Other differential diagnoses for UM are shown in *Table 1*. In general, choroidal nevi have a <5 mm basal diameter and are minimal in height, <2 mm, although several definitions of nevi have been proposed. To differentiate small UM from other choroidal pathologies, including choroidal nevi, Shields et al. formulated the mnemonic 'TFSOM', i.e. 'to find small ocular melanoma' to identify indicators of potential malignancy and predict growth.<sup>8</sup> The letters indicate Thickness >2 mm, subretinal Fluid, Symptoms, Orange

pigment and Margin to the optic disc. If none of the factors are present there is a 4 % chance of growth, while if there are one or two factors present the chance of growth rises to 36 % and >45 %, respectively.<sup>9</sup> The TFSOM mnemonic was later extended with 'Using Helpful Hints Daily' including three features, such as Ultrasound Hollowness (or low acoustic profile), absence of a Halo around the tumour and absence of Drusen.<sup>10</sup> Extraocular extension into the orbit can occur at any stage and can be detected with US, computed tomography (CT) and magnetic resonance imaging (MRI). Optical coherence tomography (OCT) and fundus autofluorescence can be useful in differentiating melanomas from other pigmented lesions (e.g. melanocytoma).<sup>11</sup> Small tumours can be measured and subretinal fluid can be observed with an OCT, whereas orange pigment can be visualised using fundus autofluorescence. Spectral domain OCT can be useful in the detection of subretinal deposits, vitreous seeding and transretinal tumour extension.<sup>12</sup> Other ancillary tests include fluorescence angiography (FAG), indocyanine green angiography (ICG), CT and MRI. The diagnostic value of FAG is limited but it can aid in differentiating UM from other lesions. The choroidal vasculature can be visualised with ICG and provides more information than FAG. Often late staining is observed because the indocyanine green leaks in the extracellular space of the tumour.<sup>13-15</sup> To detect extrascleral extension, CT and MRI are more sensitive than US.<sup>16,17</sup> However, these techniques are not routinely used in the diagnostic evaluation of UM since they are quite expensive.

### Treatment of Primary Uveal Melanoma

The treatment of UM depends on the size and location of the tumour, the secondary effects of the tumour on the eye (for instance, inflammation or neovascular glaucoma), the status of the fellow eye and the patients' choice. Over the years, eye-preserving therapies have proved to be equally effective in terms of overall patient survival and metastasis-free survival compared with radical treatment.<sup>18,19</sup> Therefore, nowadays, radical treatment or enucleation is performed in those cases with larger or advanced melanomas, or when extraocular extension is present.<sup>20</sup> A summary of the treatment modalities for UM, together with indications and complications, is listed in *Table 2*.

The most common treatment among the conservative modalities is brachytherapy. With brachytherapy or local irradiation, radioactive material is placed on the sclera at the location of the tumour. Ruthenium-106 (Ru-106) and iodine-125 (I-125) are frequently used applicators. The plaque-shaped applicator is sutured to the sclera and removed a few days later once the required dose of at least 80 Gy has been delivered to the tumour. Ru-106 applicators have a limited depth of penetration compared with I-125 applicators. Therefore Ru-106 is usually used for tumours with a maximal thickness of 7.0 mm.<sup>21,22</sup> Brachytherapy can be combined with transpupillary thermotherapy (TTT) to treat those cases with thicker tumours or to gain more tumour control if there is a suspicion that the tumour margins are not covered with brachytherapy. This is referred to as 'sandwich therapy'.<sup>23,24</sup> TTT is rarely used as a primary treatment; only those patients with small pigmented choroidal melanoma near to the fovea or optic disc may sometimes receive TTT.<sup>25</sup> After brachytherapy, radiation-induced complications can occur and include radiation retinopathy, radiation maculopathy, radiation opticopathy, vitreous haemorrhage, cataract and iris neovascularisation leading to neovascular glaucoma.<sup>26-28</sup> Local recurrences after brachytherapy have been described in 4-28 %, depending on tumour size and duration of follow up.<sup>29-32</sup> Ten to 22 % of the patients eventually have to be secondary enucleated due to radiation-induced side effects.<sup>33-36</sup>

**Table 1: Differential Diagnoses of Uveal Melanoma**

Choroidal nevus
CHRPE
Optic disc melanocytoma
Hyperplasia of the RPE
Choroidal haemangioma
Choroidal metastases
Choroidal osteoma
Peripheral exudative haemorrhagic chorioretinopathy
Hemorrhagic detachment of the retina and RPE
Choroidal haemorrhage
Posterior nodular scleritis
Intraocular leiomyoma
Adenoma of the RPE

*CHRPE = congenital hypertrophy of the retinal pigment epithelium (RPE).*

Heavy particle radiation with proton beam is available in some centres and some administer this treatment to all patients, while others reserve it for patients whose tumour is unsuitable for brachytherapy. Proton beam radiotherapy consists of several steps. First, a clip is sutured to the sclera around the base of the tumour followed by dose admission two weeks later (50-70 Gy relative biological effectiveness in 4-5 fractions).<sup>37,38</sup> Proton beam radiotherapy has some advantages compared with brachytherapy and fractionated stereotactic radiotherapy (SRT) (see below) since the dose reaches the tumour homogeneously and healthy tissue surrounding the tumour can be spared.<sup>39</sup> Proton beam radiation enables treatment of choroidal melanomas of all sizes but usually tumours up to 20 mm in diameter and 12 mm thickness are treated. When treating larger or thicker tumours with proton beam, there is a lower chance of preserving vision.<sup>40</sup> The local recurrence rate after treatment is 5 % after 10 years and this is in the same range as brachytherapy.<sup>40</sup> Secondary enucleation rates are 10-15 % due to local recurrences or complications.<sup>41,42</sup> Complications after proton beam radiotherapy include retinal detachment, neovascular glaucoma, cataract, optic neuropathy, maculopathy, vitreous haemorrhage and dryness.<sup>37</sup>

Another eye-preserving option is SRT for the treatment of small- and medium-sized posteriorly located melanomas and is becoming available in more centres. The effect of SRT on a medium-sized choroidal melanoma is depicted in *Figure 1*. One advantage of SRT compared with previously mentioned therapies, is that SRT requires no surgical procedures to determine the tumour localisation and dimensions. The tumour borders are delineated with CT and/or MRI. Stereotactic irradiation can be performed using a gammaknife, a cyberknife or a linear accelerator (LINAC). Most centres administer a total dose of 50 Gy in 4-5 fractions, although some centres prescribe higher doses.<sup>43,44</sup> Reported complications are similar to those of brachytherapy and proton beam radiotherapy and can lead to visual impairment and secondary enucleation (3-16 %).<sup>43-45</sup> Other radiogenic side effects include conjunctivitis, blepharitis or dry eye syndrome. Studies report similar local tumour control rates - 90 % 5 and 10 years after SRT.<sup>4-45</sup>

Photodynamic therapy is occasionally used as an alternative treatment for UM. The use of photosensitiser verteporfin has been described in several reports and is being more applied in amelanotic tumours.<sup>46-48</sup>

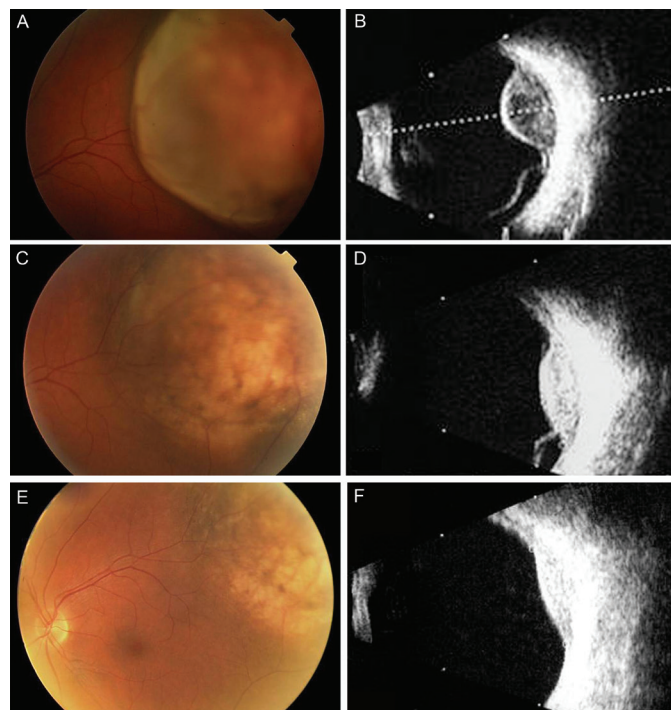
Local resection of small iris and ciliary body melanomas are widely carried out. This is not the case for choroidal melanomas. In the past, ophthalmologists were reluctant to operate on choroidal melanomas as

**Table 2: Summarised Treatment Options for Uveal Melanoma**

Treatment	Indications	Complications	SER
Brachytherapy	Small- and medium-sized tumours Thickness $\leq 7$ mm, if maximal thickness is $> 7$ mm combination with transpupillary thermotherapy	Radiation retinopathy (maculopathy) (24–40 %), papillopathy (10–14 %), vitreous haemorrhage (9–15 %), cataract (13–32 %), neovascular glaucoma (8–15 %) <sup>28,30,34,36</sup>	10–20 %
Proton beam radiotherapy	Small-, medium- and large-sized tumours LTD $\leq 20$ mm and thickness $\leq 12$ mm	Retinal detachment, vitreous haemorrhage, neovascular glaucoma (38 %), cataract (29 %), radiation retinopathy (10 %), radiation papillopathy (10 %), dry eye (24 %) <sup>40</sup>	10–15 %
Stereotactic radiotherapy	Small- and medium-sized tumours LTD $< 16$ mm, thickness $\leq 12$ mm	Radiation cataract (3–53 %), tumour vasculopathy (80 %), radiation retinopathy (5–81 %), radiation optic neuropathy (11–64 %), neovascular glaucoma (3–42 %), vitreous haemorrhage (3–33 %), retinal detachment (14–37 %), conjunctival symptoms (26 %), dry eye syndrome (8 %), eye lash loss (26 %) <sup>43–45</sup>	3–16 %
Photodynamic therapy	Amelanotic tumours		
Endoresection	Tumours ( $> 6$ –8 mm) preferably without ciliary body infiltration	Retinal detachment (9–33 %), entry site tears, cataract, acute glaucoma, choroidal neovascular membranes <sup>49,62</sup>	6 %
Exoresection	Tumours ( $> 6$ –8 mm) that are more anteriorly located (with ciliary body infiltration), tumours that are likely to develop complications with radiotherapy (e.g. neovascular glaucoma)	Retinal detachment, vitreous haemorrhage, subretinal fibrosis, cystoid macular oedema, elevated intraocular pressure, scleral thinning	4 %
Enucleation	Large-sized, advanced tumours or if extraocular extension is present LTD $> 16$ mm with thickness $> 2.0$ mm or thickness of $> 10$ mm regardless of the LTD	If extraocular extension is present, orbital recurrence can occur (10 %) <sup>63</sup>	

LTD = largest tumour diameter; SER = secondary enucleation rate.

**Figure 1: Stereotactic Radiotherapy Effect on Medium-sized Uveal Melanoma**



A: Baseline fundus photograph of uveal melanoma. The lesion is located in the upper temporal choroid 3 mm from the fovea. The best corrected visual acuity (BCVA) at baseline was 0.7; B: Baseline ultrasonography (US) shows subretinal fluid and a prominence of 6.6 mm; C: Fundus 3 months after treatment with stereotactic radiotherapy. The BCVA decreased to 0.4; D: Corresponding US 3 months later showing a decreased prominence of 4.6 mm; E: Fundus photograph 12 months after treatment showing a slightly elevated scar. The BCVA is equal to baseline measurement 0.7; F: After 12 months the tumour prominence has decreased to 2.4 mm on US.

they were concerned about manipulation of tumour cells that could lead to an increased risk of metastasis. Currently, due to improved surgical techniques and more insights on tumour progression towards metastatic disease, surgical excision is considered to be a therapeutic option for choroidal tumours. The tumour can be removed in several ways, through the vitreous and retina with a vitreous cutter, endoresection, or through a scleral opening, exoresection (e.g. iridectomy, iridocycloectomy, cyclochoroidectomy, choroidectomy). This way eyes with large melanomas, which otherwise would be enucleated, can be preserved. Surgical resection can serve as primary treatment for UM or additional to another kind of radiotherapy. Often, radiotherapy is administered prior to endoresection and exoresection is followed by treatment with brachytherapy. By using resection as a treatment, radiation-induced problems such as toxic tumour syndrome, a result of radiation-induced necrosis comprising exudative maculopathy, serous retinal detachment, rubeosis and neovascular glaucoma, can be avoided. Another advantage is that, especially with the larger melanomas, tumour tissue is available for prognostification and research. <sup>29,49,50</sup>

## Treatment of Liver Metastasis

Despite successful eradication of the ocular tumour, about 50 % of all UM patients develop metastatic disease. Metastasis spread haematogeneously to the liver and death often follows within 1 year if systemic symptoms occur. <sup>51</sup> There are no standardised therapies that improve survival in metastatic disease. Systemic treatment options, such as intravenous chemotherapy and immunotherapy, prolong life only rarely. <sup>52</sup> Systemic therapy may be more effective if administered early after diagnosis treating micrometastatic rather than macrometastatic disease. Targeted systemic therapies in metastatic UM are currently being investigated. Preclinical studies suggest potential

benefit when modulating mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase-AKT (PI3K-AKT) pathways, or receptor tyrosine kinases. The BRAF inhibitor sorafenib was administered to uveal metastatic patients in a phase II trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). A new adjuvant immunotherapy protocol has been developed, where clinical, histological and cytogenetic factors are used to identify high-risk UM patients and treat these by immunisation with their own trained dendritic cells to prevent future metastatic disease. This multicentre trial is ongoing within our Rotterdam Ocular Melanoma Study group in collaboration with the Department of Tumor Immunology of Radboud University Nijmegen.

There are several locoregional techniques available, for instance, hepatic intra-arterial chemotherapy, chemoembolisation, immunoembolisation and isolated liver perfusion. A partial hepatectomy can be beneficial in some highly selected patients. Surgery in patients with 4 or fewer metastatic lesions, more than 24 months from initial diagnosis to liver metastases and absence of miliary disease (multiple, diffuse, small-sized, dark punctuate lesions on CT) has been associated with a better outcome. A microscopically complete liver resection can increase the survival time. In a retrospective study of 255 patients who underwent surgical resection, the median overall post-operative survival was 14 months.<sup>53</sup> In patients who had a microscopically complete liver resection (compared with a microscopically or macroscopically incomplete liver resection) the survival increased to 27 months.

## Future Prospects

As mentioned above, studies investigating UM therapies with a targeted approach are ongoing. This is especially interesting since the discovery of mutations in a subset of genes in UM. A vast majority of tumours harbour either a *GNAQ* or *GNA11* ( $G\alpha$ ) mutation (up to 83 %).<sup>5</sup> These genes are involved in the MAPK pathway and mutations in the  $G\alpha$  genes are considered to be an early event in UM and not related to the tendency to metastasise.<sup>4,54,55</sup> One molecule in this pathway is MEK and several preclinical studies have investigated MEK as a potential therapeutic target.<sup>56-58</sup>

The BRCA1 associated protein 1 (*BAP1*), is mutated in up to 84 % of the metastasising UM implicating that these mutations play a role in the tumour progression.<sup>3</sup> *BAP1* plays a role in chromatin, DNA damage response and cell growth mediating deubiquitination of histone H2A and HCF1.<sup>59,60</sup> *BAP1* is located on chromosome 3p21,<sup>1</sup> and is thought to be a tumour-suppressor gene.<sup>60</sup> A recent preclinical study showed that histone deacetylase (HDAC) inhibitors can reverse the effects of *BAP1* depletion in UM cells, suggesting that HDAC inhibitors may have therapeutic potential.<sup>61</sup>

With new technologies, such as Next Generation Sequencing, more is learned about the human genome and new cancer-susceptibility genes in UM, which may serve as targets for new interventions. These molecular approaches will hopefully lead to improved patient survival. ■

- Singh AD, Damato BE, Pe'er J, et al., *Essentials of Ophthalmic Oncology*, Thorofare, NJ: Slack Incorporated, 2009;288.
- Singh AD, Turell ME, Topham AK, Uveal Melanoma: Trends in Incidence, Treatment, and Survival, *Ophthalmology*, 2011;118(9):1881-5.
- Harbour JW, Onken MD, Roberson ED, et al., Frequent mutation of BAP1 in metastasizing uveal melanomas, *Science*, 2010;330:1410-13.
- Van Raamsdonk CD, Bezrookove V, Green G, et al., Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi, *Nature*, 2009;457:599-602.
- Van Raamsdonk CD, Griewank KG, Crosby MB, et al., Mutations in GNA11 in uveal melanoma, *N Engl J Med*, 2010;363:2191-9.
- Damato B, Does ocular treatment of uveal melanoma influence survival?, *Br J Cancer*, 2010;103:285-90.
- Collaborative Ocular Melanoma Study G, Comparison of clinical, echographic, and histopathological measurements from eyes with medium-sized choroidal melanoma in the collaborative ocular melanoma study: COMS report no. 21, *Arch Ophthalmol*, 2003;121:1163-71.
- Shields CL, Shields JA, Kiratli H, et al., Risk factors for growth and metastasis of small choroidal melanocytic lesions, *Ophthalmology*, 1995;102:1351-61.
- Shields CL, Cater J, Shields JA, et al., Combination of clinical factors predictive of growth of small choroidal melanocytic tumors, *Arch Ophthalmol*, 2000;118:360-64.
- Shields CL, Furuta M, Berman EL, et al., Choroidal nevus transformation into melanoma: analysis of 2514 consecutive cases, *Arch Ophthalmol*, 2009;127:981-7.
- Schaudig U, Hassenstein A, Bernd A, et al., Limitations of imaging choroidal tumors in vivo by optical coherence tomography, *Graefes Arch Clin Exp Ophthalmol*, 1998;236:588-92.
- Heindl LM, Mardin CY, Holbach LM, et al., Vitreal seeding from uveal melanoma detected by high-resolution spectral-domain optical coherence tomography, *Arch Ophthalmol*, 2009;127:1062-4.
- Frenkel S, Barzel I, Levy J, et al., Demonstrating circulation in vasculogenic mimicry patterns of uveal melanoma by confocal indocyanine green angiography, *Eye (Lond)*, 2008;22:948-52.
- Guyon DR, Yannuzzi LA, Krupsky S, et al., Digital indocyanine-green videoangiography of intraocular tumors, *Semin Ophthalmol*, 1993;8:224-9.
- Stanga PE, Lim JJ, Hamilton P, Indocyanine green angiography in chorioretinal diseases: indications and interpretation: an evidence-based update, *Ophthalmology*, 2003;110:15-21; quiz 2-3.
- Hosten N, Bornfeld N, Wassmuth R, et al., Uveal melanoma: detection of extraocular growth with MR imaging and US, *Radiology*, 1997;202:61-7.
- Scott IU, Murray TG, Hughes JR, Evaluation of imaging techniques for detection of extraocular extension of choroidal melanoma, *Arch Ophthalmol*, 1998;116:897-9.
- Seddon JM, Gragoudas ES, Albert DM, et al., Comparison of survival rates for patients with uveal melanoma after treatment with proton beam irradiation or enucleation, *Am J Ophthalmol*, 1985;99:282-90.
- Seddon JM, Gragoudas ES, Egan KM, et al., Relative survival rates after alternative therapies for uveal melanoma, *Ophthalmology*, 1990;97:769-77.
- Spagnolo F, Caltabiano G, Queirolo P, Uveal melanoma, *Cancer Treat Rev*, 2012;38:549-53.
- Bergman L, Nilsson B, Lundell G, et al., Ruthenium brachytherapy for uveal melanoma, 1979-2003: survival and functional outcomes in the Swedish population, *Ophthalmology*, 2005;112:834-40.
- Damato B, Patel I, Campbell IR, et al., Local tumor control after 106Ru brachytherapy of choroidal melanoma, *Int J Radiat Oncol Biol Phys*, 2005;63:385-91.
- Bartlema YM, Oosterhuis JA, Journee-De Korver JG, et al., Combined plaque radiotherapy and transpupillary thermotherapy in choroidal melanoma: 5 years' experience, *Br J Ophthalmol*, 2003;87:1370-73.
- Pe'er J, Ruthenium-106 brachytherapy, *Dev Ophthalmol*, 2012;49:27-40.
- Shields CL, Shields JA, Perez N, et al., Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations, *Ophthalmology*, 2002;109:225-34.
- Gragoudas ES, Li W, Lane AM, et al., Risk factors for radiation maculopathy and papillopathy after intraocular irradiation, *Ophthalmology*, 1999;106:1571-7; discussion 7-8.
- Kinyoun JL, Lawrence BS, Barlow WE, Proliferative radiation retinopathy, *Arch Ophthalmol*, 1996;114:1097-100.
- Suwanman P, Immonen I, Kivela T, et al., Radiation related complications after ruthenium plaque radiotherapy of uveal melanoma, *Br J Ophthalmol*, 1996;80:732-9.
- Damato B, Foulds WS, Indications for trans-scleral local resection of uveal melanoma, *Br J Ophthalmol*, 1996;80:1029-30.
- Gragoudas ES, 1996 Jules Gonin Lecture of the Retina Research Foundation, Long-term results after proton irradiation of uveal melanomas, *Graefes Arch Clin Exp Ophthalmol*, 1997;235:265-7.
- Seregard S, aft Trampe E, Lax I, et al., Results following episcleral ruthenium plaque radiotherapy for posterior uveal melanoma. The Swedish experience, *Acta Ophthalmol Scand*, 1997;75:11-16.
- Wilson MW, Hungerford JL, Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma, *Ophthalmology*, 1999;106:1579-87.
- Bell DJ, Wilson MW, Choroidal melanoma: natural history and management options, *Cancer Control*, 2004;11:296-303.
- Gunduz K, Shields CL, Shields JA, et al., Radiation complications and tumor control after plaque radiotherapy of choroidal melanoma with macular involvement, *Am J Ophthalmol*, 1999;127:579-89.
- Lommatzsch PK, Werschnik C, Schuster E, Long-term follow-up of Ru-106/Rh-106 brachytherapy for posterior uveal melanoma, *Graefes Arch Clin Exp Ophthalmol*, 2000;238:129-37.
- Tjho-Heslinga RE, Davelaar J, Kemme HM, et al., Results of ruthenium irradiation of uveal melanomas: the Dutch experience, *Radiother Oncol*, 1999;53:133-7.
- Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, et al., Treatment of uveal melanoma by accelerated proton beam, *Dev Ophthalmol*, 2012;49:41-57.
- Gragoudas ES, Lane AM, Regan S, et al., A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma, *Arch Ophthalmol*, 2000;118:773-8.
- Weber DC, Bogner J, Verwey J, et al., Proton beam radiotherapy versus fractionated stereotactic radiotherapy for uveal melanomas: A comparative study, *Int J Radiat Oncol Biol Phys*, 2005;63:373-84.
- Conway RM, Poothullil AM, Daftari IK, et al., Estimates of ocular and visual retention following treatment of extra-large uveal melanomas by proton beam radiotherapy, *Arch Ophthalmol*, 2006;124:838-43.
- Egan KM, Ryan LM, Gragoudas ES, Survival implications of enucleation after definitive radiotherapy for choroidal melanoma: an example of regression on time-dependent covariates, *Arch Ophthalmol*, 1998;116:366-70.
- Egger E, Zografos L, Schalenbourg A, et al., Eye retention after proton beam radiotherapy for uveal melanoma, *Int J Radiat Oncol Biol Phys*, 2003;55:867-80.
- Krema H, Somani S, Sahgal A, et al., Stereotactic radiotherapy for treatment of juxtapapillary choroidal melanoma: 3-year follow-up, *Br J Ophthalmol*, 2009;93:1172-6.
- Muller K, Nowak PJ, de Pan C, et al., Effectiveness of fractionated stereotactic radiotherapy for uveal melanoma, *Int J Radiat Oncol Biol Phys*, 2005;63:116-22.
- Zehetmayer M, Kitz K, Menapace R, et al., Local tumor control and morbidity after one to three fractions of stereotactic external beam irradiation for uveal melanoma, *Radiother Oncol*, 2000;55:135-44.
- Canal-Fontcuberta I, Salomao DR, Robertson D, et al.,

- Clinical and histopathologic findings after photodynamic therapy of choroidal melanoma, *Retina*, 2012;32:942–8.
47. Barbazetto IA, Lee TC, Rollins IS, et al., Treatment of choroidal melanoma using photodynamic therapy, *Am J Ophthalmol*, 2003;135:898–9.
  48. Donaldson MJ, Lim L, Harper CA, et al., Primary treatment of choroidal amelanotic melanoma with photodynamic therapy, *Clin Experiment Ophthalmol*, 2005;33:548–9.
  49. Damato BE, Local resection of uveal melanoma, *Dev Ophthalmol*, 2012;49:66–80.
  50. Robertson DM, Melanoma endoresection: a perspective, *Retina*, 2001;21:403–7.
  51. Eskelin S, Pyrhonen S, Hahka-Kemppinen M, et al., A prognostic model and staging for metastatic uveal melanoma, *Cancer*, 2003;97:465–75.
  52. Augsburger JJ, Correa ZM, Shaikh AH, Effectiveness of treatments for metastatic uveal melanoma, *Am J Ophthalmol*, 2009;148:119–27.
  53. Mariani P, Piperno-Neumann S, Servois V, et al., Surgical management of liver metastases from uveal melanoma: 16 years' experience at the Institut Curie, *Eur J Surg Oncol*, 2009;35:1192–7.
  54. Bauer J, Kilic E, Vaarwater J, et al., Oncogenic GNAQ mutations are not correlated with disease-free survival in uveal melanoma, *Br J Cancer*, 2009;101:813–15.
  55. Onken MD, Worley LA, Long MD, et al., Oncogenic mutations in GNAQ occur early in uveal melanoma, *Invest Ophthalmol Vis Sci*, 2008;49:5230–34.
  56. Ambrosini G, Pratilas CA, Qin LX, et al., Identification of unique MEK-dependent genes in GNAQ mutant uveal melanoma involved in cell growth, tumor cell invasion, and MEK-resistance, *Clin Cancer Res*, 2012;18(13):3552–61.
  57. Ho AL, Musi E, Ambrosini G, et al., Impact of Combined mTOR and MEK Inhibition in Uveal Melanoma Is Driven by Tumor Genotype. *PLoS One*, 2012;7:e40439.
  58. Mitsiades N, Chew SA, He B, et al., Genotype-dependent sensitivity of uveal melanoma cell lines to inhibition of B-Raf, MEK, and Akt kinases: rationale for personalized therapy. *Invest Ophthalmol Vis Sci*, 2011;52:7248–55.
  59. Jensen DE, Proctor M, Marquis ST, et al., BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression, *Oncogene*, 1998;16:1097–112.
  60. Ventii KH, Devi NS, Friedrich KL, et al., BRCA1-associated protein-1 is a tumor suppressor that requires deubiquitinating activity and nuclear localization, *Cancer Res*, 2008;68:6953–62.
  61. Landreville S, Agapova OA, Matatall KA, et al., Histone deacetylase inhibitors induce growth arrest and differentiation in uveal melanoma, *Clin Cancer Res*, 2012;18:408–16.
  62. Garcia-Arumi J, Zapata MA, Balaguer O, et al., Endoresection in high posterior choroidal melanomas: long-term outcome, *Br J Ophthalmol*, 2008;92:1040–45.
  63. Affeldt JC, Minckler DS, Azen SP, et al., Prognosis in uveal melanoma with extrascleral extension, *Arch Ophthalmol*, 1980;98:1975–9.