Practice guidelines in the management of uveal melanoma

J.-F. Baurain, P. de Potter

Uveal melanoma is a rare oncological disease. This incidence has remained stable for the past 50 years. There is no survival difference depending on the type of ocular treatment (enucleation versus radiotherapy versus tumour resection). Brachytherapy (Ru-106, I-125) presently remains the most common method for treating uveal melanoma. Despite adequate and early local treatment, half of the patients will develop metastatic recurrence with an average of 2.5 years after initial diagnosis. Clinical and histological prognostic factors have been identified, but some studies suggest that inactivation of BAP1 by chromosomal deletion or mutation is a key event driving metastasis development. Presently, no adjuvant treatment prevents those metastatic relapses. Nearly 90% of patients who relapse have only liver metastases. The median survival of those patients is about four months. Numerous trials evaluating the interest of exclusive liver treatment have failed to demonstrate an increase in survival, except surgery for solitary liver metastasis. Chemotherapy with dacarbazine remains the standard treatment of metastatic patients. New treatments targeting the signal transduction pathways or aiming at the stimulation of the immune system are under development.

(Belg J Med Oncol 2013;7:20-26)

Introduction

Uveal (iris, ciliary body and choroid) melanoma is the most common primary intra-ocular malignant tumour with a reported incidence ranging from 4.3 to 10.9 new cases per million per year. This incidence has remained stable for the last 50 years.[1]

The goals of ocular treatment of uveal melanoma are to prevent metastatic spread and to conserve the eye with useful vision, if possible. As the Collaborative Ocular Melanoma Study (COMS) or other non-randomised comparative studies have shown no significant survival difference between enucleation and conservative ocular treatments, saving the eye as long as possible remains a logical therapeutic approach for the ocular oncologist.[2]

Up to 50% of the patients will develop metastatic recurrence on average 2.5 years after initial diagnosis. Metastatic disease is always fatal. It is important to note that there are late recurrence cases up to ten years after diagnosis. The development of metastatic disease is highly variable ranging from dazzling to relative indolence. The disease is rarely stable and spontaneous regression is lacking, in contrast to cutaneous melanoma.

Authors: J.-F. Baurain MD PhD[1], P. de Potter MD PhD[2]. [1]Department of Medical Oncology, Centre du Cancer, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium, [2]Department of Ophtalmology, Centre du Cancer, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium.

Please send all correspondence to: J.-F. Baurain MD PhD, Department of Medical Oncology, Centre du Cancer, Cliniques universitaires Saint-Luc, Université catholique de Louvain, 10 avenue Hippocrate, 1200 Brussels, Belgium, tel. nr.: +32 2 764 8300, e-mail: jf.baurain@uclouvain.be.

Conflict of interest: the authors have nothing to disclose and indicate no potential conflicts of interest.

Keywords: uveal melanoma, ocular oncology, brachytherapy, genetics.

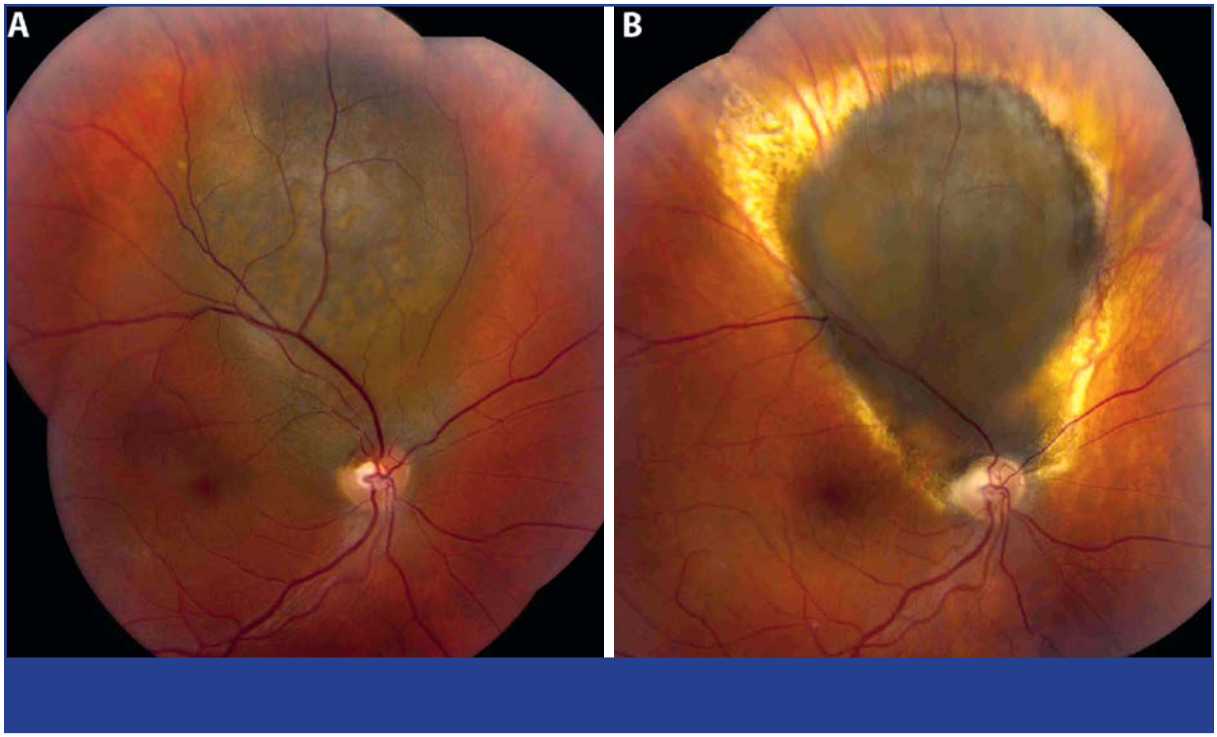

Figure 1. Primay uveal melanoma with a juxtapapillary location and overhanging the superior edge of the optic disc before treatment with custom-designed I-125 plaque (A). After treatment, tumour shrinkage is documented without covering the optic disc (B).

Ocular management of uveal melanoma

Uveal melanomas can be conservatively treated by various forms and combinations of radiotherapy, thermotherapy and tumour resection which need to be tailored to the skills of the ocular oncologists and surgeons, and tumour size, location, extent as well as patients' needs, fears, or expectations, and the possibility for the patient and the ophthalmologist to access those treatment modalities. These conservative methods include transpupillary thermotherapy, different forms of radiotherapy (episcleral plaque radiotherapy, proton beam radiotherapy, stereotactic radiotherapy), and tumour resection.

Even now, when the majority of uveal melanomas in developed countries are managed with various eye-conserving modalities, enucleation still remains a common alternative.[3] Primary enucleation for uveal melanoma is currently performed when other methods are considered unlikely to conserve the eye and useful vision without causing excessive morbidity; and /or if the patient is not motivated to try to save the eye. Overall enucleation is currently performed in about 35% of all patients with uveal melanoma among different ocular oncology centres, mostly because patients present at a late stage. In a parallel study, the COMS also discovered that pre-enucleation irradiation of a large tumour does not offer survival benefit over enucleation alone.[4]

Transpupillary thermotherapy (TTT) is effective as primary treatment of strictly selected small and medium-sized choroid melanomas (pigmented choroid tumours with a diameter up to 12 mm, not exceeding 4.0 mm in thickness, minimal overlying subretinal fluid and a retro-equatorail location).[5,6] In most instances, TTT is currently applied as adjuvant treatment to plaque radiotherapy, charged particles radiotherapy or local tumour resection since viable intrascleral tumour cells may be the source of tumour recurrence when TTT is used as primary treatment.[7]

Brachytherapy is the most common method for treating uveal melanoma and currently the ruthenium-106 (Ru-106) and iodine-125 (I-125) applicators are the most frequently used. The Ru-106 isotope is a beta ray emitter and as such has a limited depth penetration and Ru-106 plaques are ideally reserved for tumours with a maximal thickness of up to 7.0 mm.[8] I-125 plaques (γ-radiation) can successfully treat tumours

as thick as 12mm.[9] Custom-designed I-125 plaque can be used for non-resectable iris melanomas, choroid melanomas with juxtapapillary location, and extra-large tumours with a basal diameter up to 20mm (*Figure 1*). Most radiation-related ocular side-effects (cataract, optic neuropathy, retinopathy, neovascular glaucoma, scleral necrosis) occur within the first postoperative years.[10] Significant loss of vision following brachytherapy is associated with reduced initial visual acuity before treatment, greater tumour height and proximity to the fovea and the optic disc.[9,10] The overall tumour recurrence rate is reported to be between 4 and 10% at five years according to different clinical studies. Local tumour recurrence after plaque radiotherapy is weakly associated with reduced survival. The probability of ocular conservation depends on many factors (large tumour diameter and thickness, associated retinal detachment, posterior tumour extension). Generally, eyes are enucleated following episcleral plaque radiotherapy in 5-15% of patients at 3-5 years follow-up.[11]

Proton beam irradiation of uveal melanoma has some advantages compared to brachytherapy because of the homogenous doses administered to the tumour and the possibility of sparing normal ocular tissue close to the tumour. However, the use of proton beam radiotherapy has been limited by the lack of availability of proton facilities and the high cost of the treatment. Standard treatment protocols evolve with more sophisticated radiotherapy techniques and changes in dose administration (presently 60 Gy cobalt relative biological effectiveness in 4 fractions).[12,13] The 10-year cumulative rate of tumour regrowth was reported to be 5% and the probability of retaining the eye treated with proton radiation at 10 years 12%.[14] Tumour characteristics that increase the risk of enucleation include height, proximity to optic disc and fovea and tumour diameter. Reports of ocular morbidity and preservation of vision comparing brachytherapy to proton beam radiotherapy show no clear advantages in favour of each method. However, the incidence of anterior segment complications such as keratoconjunctivitis sicca, loss of eye lashes, cataract and neovascular glaucoma is statistically higher with proton irradiation than with plaque radiotherapy.[15]

Stereotactic radiotherapy is a novel approach to the radiotherapy of uveal melanoma which includes single-fraction stereotactic radiosurgery (SRS), using a Gamma Knife as well as more recently a cyberknife and fractionated stereotactic radiotherapy (SRT) with linear accelerator (LINAC) using a hypofractionated scheme of 4-5 fractions and total doses between 50 and 70 Gy.[16,17] Radiogenic side-effects after SRT are reported similarly to other forms of radiotherapy Early results are encouraging with high rates of local tumour control (>90%) but additional studies with larger samples of patients and longer follow-up are indicated.

Local resection of uveal melanoma is aimed to remove the tumour en bloc through a scleral opening as a exoresection procedure (trans-scleral choroidectomy – ciliochoroidectomy), particularly in cases where the tumour is considered unsuitable for radiotherapy or in a piecemeal fashion with a vitreous cutter during a vitrectomy procedure (endoresection).[18] Both exoresection and endoresection can be undertaken as a primary procedure, or in combination with any form of radiotherapy, or after radiotherapy for recurrent or toxic tumour.[18,19] Therefore, it is only performed in a few centres with experienced vitreoretinal surgeons and reserved for highly motivated patients.

Adjuvant treatment after ocular management

Monosomy of chromosome 3 is a bad prognosis marker known for over ten years. Recently, a tumour suppressor gene located on the short arm of chromosome 3 was identified. The function of the encoded protein BAP1 (BRCA Associated Protein 1) is not precisely known. Interestingly, somatic mutations inactivating BAP1 were found in 84% of ocular melanoma metastases.[20] All these instances suggest that inactivation of BAP1 by chromosomal deletion and/or mutation is a key event driving metastasis development. BAP1 mutations and chromosome 3 status are markers used as stratification factors in clinical trials assessing efficacy of an adjuvant treatment but not in routine practice.

No guideline is available to help us in the follow-up of uveal melanoma patients. The impact of a regular follow-up on the increase of overall survival (OS) of these patients has not been demonstrated. However, it is common practice to carry out biological and

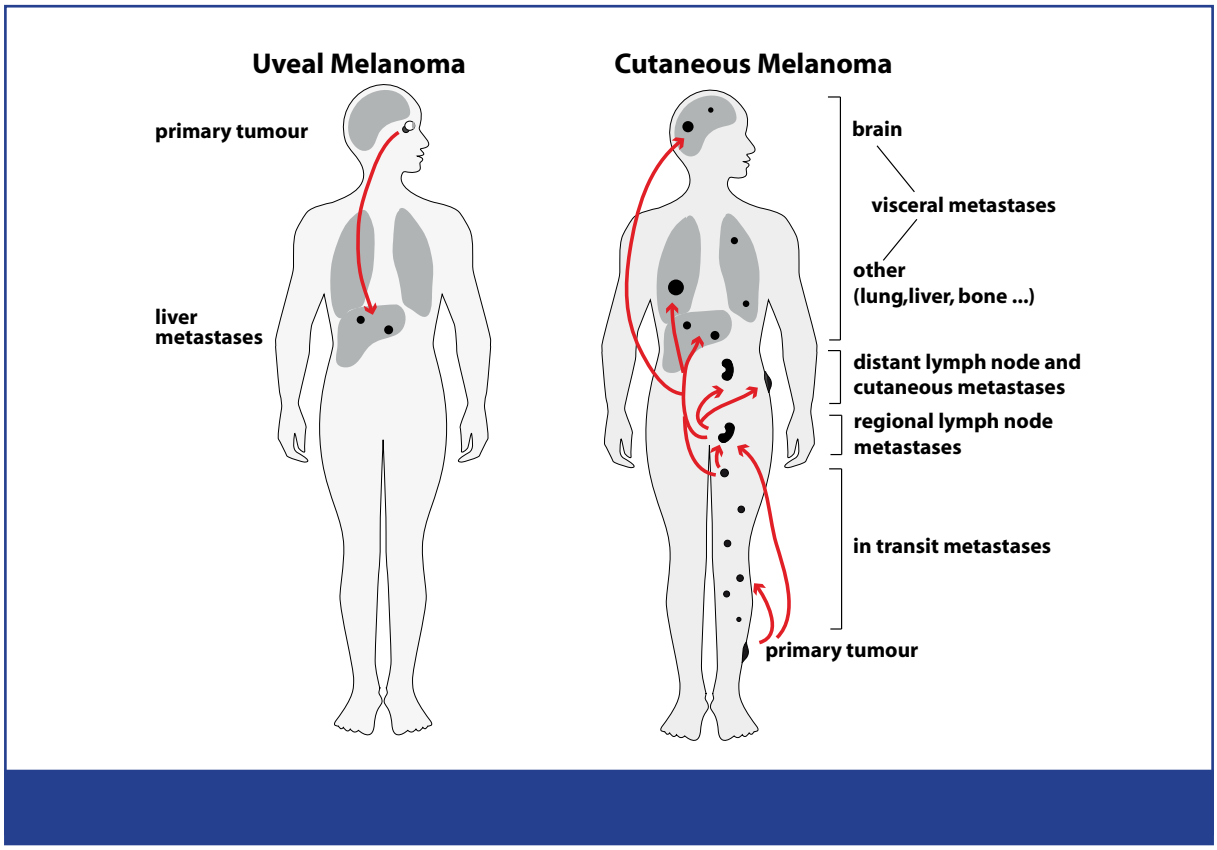

Figure 2. Routes of dissemination of uveal melanoma compared to cutaneous melanoma.

radiological controls every six months until the tenth year. At our institution, every six months we perform a blood test, chest radiography and liver ultrasound. If a suspicious laesion is discovered, a CT scan, a liver MRI or a PET scan is performed.

The particularity of uveal melanoma is its mode of spread that is different from his first cousin cutaneous melanoma. In 90% of the cases, the uveal melanoma metastasises exclusively in the liver (*Figure 2*). The biological reasons for this tropism are totally unknown to date. This unique mode of spread has led some teams to offer hepatic intra-arterial adjuvant chemotherapy to patients with a tumour showing a monosomy 3. The results of this study are expected shortly. Another appealing approach is the anti-tumour vaccination. We know that it has no or few side-effects. Here also, clinical studies are under development. Currently, no adjuvant therapy is available to reduce the risk of recurrence.

Recently, we analysed the survival of over 700 Belgian patients treated and followed-up in our institution.[21] These results were presented at the World Congress of Ocular Oncology in Argentina. OS of our patients is excellent with 83% of patients alive at ten years. We also observed that the systemic recurrence rate was 14%, which is well below what is reported in the literature for equivalent TNM stages (30%). Multivariate analysis showed that risk factors for developing recurrence were similar to those reported in the literature: age (p=0.002), tumour size (p=0.035) and epithelioid histology (p=0.002). We are currently analysing the reasons for this difference in the incidence of recurrence. One hypothesis would be the speed of the management of the primary tumour along with optimised radiation therapy.

Management of the metastatic disease

Nearly 90% of patients who relapse have only liver metastases. Median survival without treatment ranges from two to six months. The standard treatment is chemotherapy with an alkylating agent such as dacarbazine or fotemustine. It does not increase survival in patients who remain alive on average five to seven months. Since the uveal melanoma has this unique feature to give almost exclusively liver metastases, locoregional treatments have been tried. The first option is surgery of solitary liver metastasis.

Admittedly, this would increase the survival of these patients a few months but this clinical situation is very rare. Therefore, treatments of hepatic chemo-embolisation with cisplatin have been proposed with a response rate of 46% and a median survival of eleven months.[22] Studies evaluating the interest of isolated liver perfusion with melphalan or TNF were performed. The response rate was around 62% but the appearance of extrahepatic metastases was common and no benefit in survival was observed.[23] The EORTC has recently completed a randomised clinical trial where intravenous chemotherapy was compared to the hepatic arterial chemotherapy. Indeed, preliminary results with fotemustine given directly in the liver via the hepatic artery showed that nearly 40% of patients responded to treatment and their survival was increased by almost six months. The difficulty of intra-arterial chemotherapy is the placement of the catheter in the hepatic artery. The results of this study were presented at ASCO this year.[24] The response rate is slightly increased in patients receiving intra-arterial chemotherapy but no increase in survival is observed. Therefore, this therapeutic approach can be abandoned. In our institution, we are currently studying selective hepatic radiotherapy. The principle is to inject small radioactive beads, called Sir-spheres, in the hepatic artery. These beads are immobilised in the tortuous vessels of tumours, irradiating them in a targeted way. This therapy is already being used in liver metastases of colorectal cancers with some success.[25]

The last twenty years of research show that the chosen treatment of metastatic uveal melanoma is chemotherapy administered intravenously (dacarbazine 1x/3sem). Recently, ipilimumab was shown to increase the survival of patients with metastatic cutaneous melanoma.[26] We gave ipilimumab to eleven patients with metastatic uveal melanoma progressing after at least one line of chemotherapy. We observed one late clinical response, one mixed response and one patient showed a stabilisation of the disease. The median survival of these patients was six months. A randomised study should confirm these encouraging results before it can be an accepted treatment.

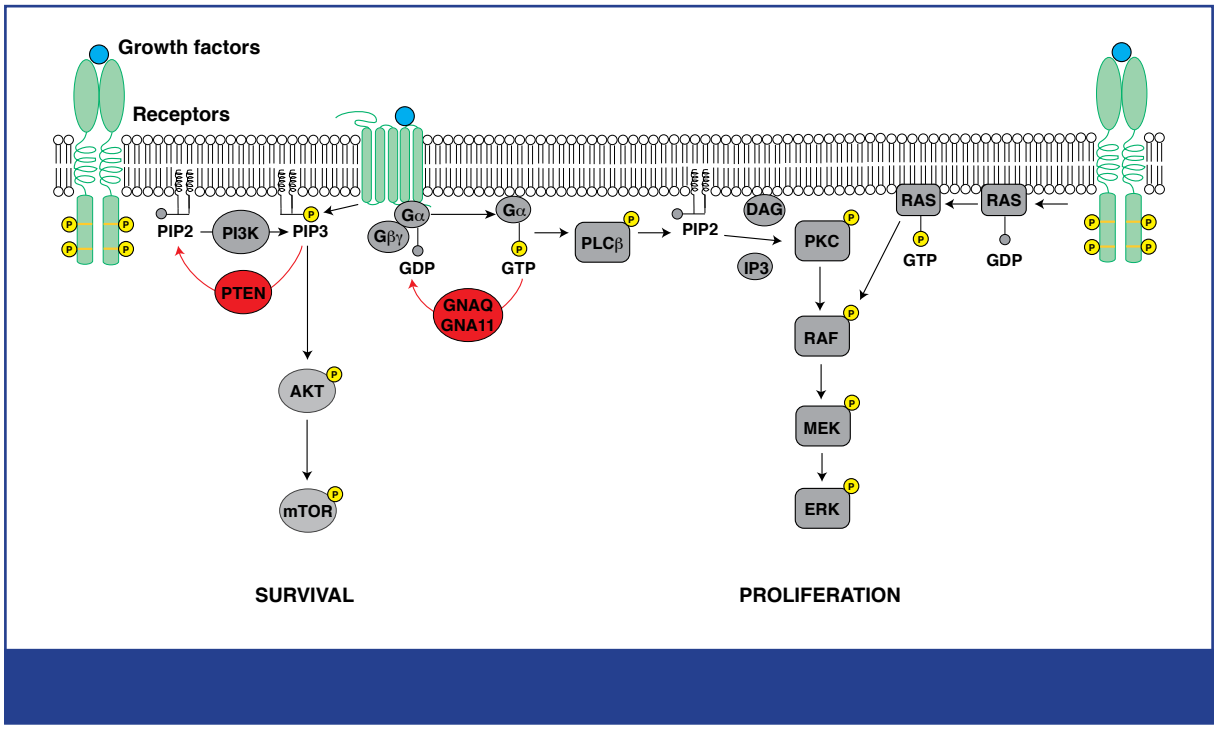

Figure 3. Signal transduction pathways in melanoma cells. There are various growth factor receptors on the surface of melanoma cells of which receptors tyrosine kinase and G protein-coupled receptors Activation of these receptors stimulates the MAP kinase pathway (RAS/RAF/MEK) and the PIP3 kinase pathway (PIP3K/AKT/mTOR). The PTEN, GNA11, GNAQ proteins can inhibit signal transduction. PTEN is frequently lost in melanomas. While GNAQ and GNA11 are frequently mutated in uveal melanomas thus losing their functionality.

Genome sequencing of uveal melanoma has not revealed mutations in genes encoding proteins of the MAPK signaling pathway (RAS, RAF) in contrast to cutaneous melanoma. In addition, very few mutations are found in ocular melanoma. The oncogenesis of these tumours seems quite different from that of their namesake. In 83% of cases, the sequencing of the genome showed the presence of mutations in the genes coding for the phosphatises GNAQ and GNA11.[27] These are the alpha subunits of G proteins involved in the inhibition of signal transduction (*Figure 3*). The mutations proved to inhibit protein function. The result is an indirect activation of signal transduction of growth factor receptors. This feature may be a therapeutic lead. Clinical studies are underway to study the effectiveness of MEK and PKC inhibitors in metastatic ocular melanoma.

Conclusion

Survival after treatment of uveal melanoma probably does not depend on the method of treatment but rather on many clinical, histological and genetic risk factors. The conservative therapeutic modalities can be administrated individually or in various combinations to enhance the success of local tumour control and minimise the risk of collateral damages to the non-involved ocular structures. Further studies investigating the impact of ocular treatment on survival should include only patients whose prognosis can be estimated according to the clinical stage, histological grade and genetic type. However, the indications and contraindications as well as safety of biopsy of uveal melanoma remain under debate. Moreover, up to now no treatment after local management protects the patients against a relapse. Although preferably treatment selection of the primary or the metastatic uveal melanoma should be evidence-based, the required evidence is either inadequate or completely lacking. Therefore, the patients should be treated in experienced multidisciplinary teams that must include these patients in clinical trials.

References

1. Virgili G, Gatta G, Ciccolallo L, et al. Incidence of uveal melanoma in Europe. Ophthalmology 2007;114:2309-15.
2. Collaborative Ocular Melanoma Study.Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No.28. Arch Ophthalmol 2006;124:1684-93.
3. Damato BE, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach to treatment: an audit of 1632 patients. Ophthalmology 2004;111:977-83.
4. The Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized tril of pre-enucleation radiation of large choroidal melanoma II: initial mortality findings. COMS report no. 10. Am J Ophthalmol 1998;125:779-96.
5. Shields CL, Shields JA, Perez N, et al. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases. Ophthalmology 2002;109:225-34.
6. De Potter P, Jamart J. Adjuvant indocyanine green in transpupillary thermotherapy for choroidal melanoma. Ophthalmology 2003;110:406-14.
7. Shields CL, Cater J, Shields JA, et al. Combined plaque radiotherapy and transpupillary thermotherapy for choroidal melanoma. Arch Ophthalmol 2002;120:933-40.
8. Pe'er J. Ruthenium-106. In: Jager MJ et al, editors. Current Concepts in Uveal Melanoma. Basel, Karger, 2012;49:27-40.
9. Puusaari I, Heikkonen J, Summanen P, et al. Iodine brachytherapy as an alternative to enucleation for large uveal melanomas. Ophthalmology 2003;110:2223-34
10. Puusaari I, Heikkonen J, Kivela T. Ocular complications after iodine brachytherapy for large uveal melanoma. Ophthalmology 2004;111:1768-77.
11. Jampol LM, Moy CS, Murray TG, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report No 19. Ophthalmology 2002;109:2197-206.
12. Gragoudas ES, Lane AM. Uveal melanoma: proton beam irradiation. Ophthalmol Clin North Am 2005;18:111-8.
13. Desjardins L, Lumbroso L, levy C, et al. Treatment of uveal melanoma by accelerated proton beam. In: Jager MJ et al, editors. Current Concepts in Uveal Melanoma. Basel, Karger, 2012;49:41-57.
14. Gragoudas ES, Lane AM, Munzenrider J, et al. Long-term risk of local failure after proton therapy for choroidal/ciliary body melanoma. Trans Am Ophthalmol Soc 2002;100:43-8.
15. Egger E, Schalenbourg A, Zografos L, et al. Eye retention after proton

Key messages for clinical practice

Treatment selection for uveal melanoma is difficult and should remain in the hands of skilled ocular and medical oncologists. They will be able to discuss the various options and modalities in a multidisciplinary approach objectively with the patient.

beam radiotherapy for uveal melanoma. Int J Radiat Oncol Biol Phys 2003;55:867-80.

16. Zytkovicz A, Daftari I, Philipps TL, et al. Peripheral dose in ocular treatments with CyberKnife and gamma Knife radiosurgery compared to proton radiotherapy. Phys Med Biol 2007;52:5957-71.

17. Dieckmans K, Georg D, Bogner J, et al. Optimizing LINAC-based stereotactic radiotherapy for uveal melanoma: 7years' clinical experience. Int J Radiat Oncol Biol Phys 2006;66:47-52.

18. Damato B. Local resection of uveal melanoma. In Jager MJ et al, editors. Current Concepts in Uveal Melanoma. Basel, Karger, 2012;49:66-80.

19. Puusaari I, Damato B, Kivelä T. Transscleral local resection versus iodine brachytherapy for uveal melanomas that are large because of tumour height. Graefes Arch Clin Exp Ophthalmol 2007;245:522-33.

20. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science 2010;330(6009):1410-3.

21. Hammouch F, De Potter P, Renard L, et al. Incidence of metastatic disease and survival of 716 consecutive patients with posterior uvéal melanoma: a retrospective monocentric study. ISOO 2011;1617.

22. Mavligit GM, Charnsangavej C, Carrasco CH, et al. Regression of ocular melanoma metastatic to the liver after hepatic arterial chemoembolization with cisplatin and polyvinyl sponge. JAMA 1988;260(7):974-6.

23. Feldman ED, Pingpank JF, Alexander HR Jr. Regional treatment options for patients with ocular melanoma metastatic to the liver. Ann Surg Oncol 2004;11(3):290-7.

24. Leyvraz S, Suciu S, Piperno-Neumann S, et al. Randomized phase III trial of intravenous (IV) versus hepatic intra-arterial (HIA) fotemustine in patients with liver metastases from uveal melanoma: Final results of the EORTC 18021 study. J Clin Oncol 30, 2012 (suppl; abstr 8532).

25. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol 2010;28(23):3687-94.

26. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364(26):2517-26.

27. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11 in uveal melanoma. N Engl J Med 2010;363(23):2191-9.