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Review paper

# CURRENT CONCEPTS IN THERAPY OF UVEAL MELANOMA

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***Abstract:*** There has been significant progress made in the diagnosis and treatment of the primary uveal melanoma during the past decades and despite that, survival rate of uveal melanoma patients is still stable. Treatment options for uveal melanoma include phototherapy, brachytherapy, proton beam therapy, stereotactic radiotherapy, local resection, anti-angiogenic therapy, immunotherapy, and enucleation. Genetic analysis of tumors provides us with valuable prognostic information although effective therapies are lacking at this moment. It is not established yet whether prolonged survival is the result of treatment or whether it merely reflects earlier detection of metastases. Also, there are indications that 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. New studies are needed to provide a better understanding of of ocular treatment impact on survival in patients whose prognosis can be estimated according to the clinical stage, histological grade and genetic type. Therefore, the patients should be treated in experienced multi-disciplinary teams that must include these patients in clinical trial.

***Keywords:*** uveal melanoma, therapy, immunotherapy, metastatic disease.

## INTRODUCTION

Although uveal melanoma represents only 5% of all melanomas, it is one of the most deadly diseases in ophthalmology and, is the most common primary intraocular malignancy in adults, with incidence rate of 7.0 cases per 1. 000.000 people (in Caucasian population) which has remained stable over the last half century (1). It originates from neural crest derived melanocytes of the uvea and can be located either in the choroid (72%), in the ciliary body (23%) or in the iris (5%) (2). Despite significant improvement in the diagnosis and treatment of the primary tumor, the survival rate of uveal melanoma patients has not improved since the early 70s. Half of the patients will develop metastatic recurrence with an average of 2.5 years after initial diagnosis. Half of all patients die of, most often late appearing, metastatic disease (15-year survival: 53%) (2, 3). Uveal melanomas metastasize almost exclusively by haematogenous route. Most of patients (about 90%) with metastatic disease have hepatic metastases. Less frequent it metastasizes to the lung, skin, bone and brain (4). Regional lymphatic dissemination does is rare, owing to an absence of lymphatic drainage of the ocular interior. Despite significant improvements in the diagnosis and treatment protocols of the primary tumor, there are currently no effective therapies for metastatic uveal melanoma. Current studies evaluate mechanisms underlying the metastatic process, including tumor vasculature, cytogenetics, oncogene activation, immunology, melanoma-associated antigens and tumor cell migration. New treatments based on this knowledge are under development with a goal to develop effective therapies (5).

## Ocular management of uveal melanoma

Patients with uveal melanoma are faced with many serious threats: visual loss and all the consequences of impaired function; painful ocular morbidity; loss of the eye, with all the social implications of any disfigurement; and early death from cancer. Fortunately, there has been enormous progress in the management of patients with uveal melanoma. The quality of life of these patients is therefore better than might be expected. Management involves tumour detection; diagnosis; patient counselling and care planning; treatment of the ocular tumour; detection and treatment of local tumour recurrence and other ocular complications; prognostication; psychological support; screening for met-

astatic disease, if appropriate; and treatment of metastases (6).

Treatment options for uveal melanoma include phototherapy, brachytherapy, proton beam therapy, stereotactic radiotherapy, local resection, biopsy, anti-angiogenic therapy, immunotherapy, and enucleation.

## Phototherapy

Because of a high-rate of complications (retinal traction and detachment, vascular occlusion, choroidal neovascularisation, and local tumour recurrence), formerly used xenon arc and Argon laser photocoagulation, are no longer in use. Transpupillary thermotherapy, developed when infrared lasers became available, is more effective and safer than photocoagulation but is associated with a significant rate of local tumour recurrence and is therefore used mostly as an adjunct to radiotherapy. The development of Verteporfin in the 1990s, encouraged Heimann and Damato (and others elsewhere) to treat more patients with photodynamic therapy. This treatment is still under investigation (7).

## Brachytherapy

Brachytherapy is the most common conservative method of treating uveal, mainly posterior uveal melanoma, using radioactive applicators, iodine-125 (I-125) or ruthenium-106 (Ru-106) plaque. Exception are tumors that grow over or into the optic nerve and large tumors, with a diameter of 20 mm or larger and/or thickness of 10 mm or more. I-125 plaques with deeper radiation penetration (emit gamma radiation), making it possible to treat large tumours (up to 10 mm in height). Ru-106 plaques (emit beta radiation), with their more limited depth of penetration, are usually used for tumors with a maximal thickness of up to 7 mm (8). The main advantage of Ru-106 over other isotopes is the less damage it causes to the healtha part of the eye and the better preservation of the vision. Although most uveal melanomas treated with Ru-106 brachytherapy exhibit a significant reudction in size, immunohistochemical analysis of such irradiated tumors, showed proliferating activity, which was significantly lower and did not regrow compared to tumors that regrew and were not treated by irradiation at all. The tumor recurrence rate varies significantly among ocular oncology centers and it was not found to be associated with radiation dose or radiation rate to the tumor base or apex. Eye with tumor recurrence will be treated by additional brachytherapy or will be enuclated when additional brachytherapy is not possible. he most common complications are cataract, radiation retinopathy and maculopathy, irradiation optic neuropathy, vitreous hemorrhage, and iris neovascularisation leading in most cases to neovascular glacuoma. Combined Ru-106 brachytherapy and transpupillary thermotherapy for treating uveal melanoma is sometimes used (9).

## Proton beam radiotherapy

Proton beam therapy of uveal melanoma is one of the best treatment modalities allowing excellent tumor control and good survival, but thebelevated costs and very few centers available around the world limit the access to this effective modality. Proton beam therapy has the advantage of delivering a homogenous dose to the entire tumor, whereas in brachytherapy the tumor base receives several times the dose of the tumor apex. This is achieved by the physical properties of the accelerated proton particles, as once the calculated dose is delivered to the target tissue, there is a sharp fall of radiation dose, which is called the Bragg peak phenomenon which allows sparing of normal surrounding tissues (10). Approximately 70% of the radiation dose to the tumor is deposited in the anterior segment, and therefore adnexal and anterior segment side effects, such as eyelash loss, dry eye, keratitis, corneal ulceration, iris neovascularization and neovascular glaucoma, iridocyclitis, cataract, retinal are more common after treatment with proton beam radiation therapy (compared to low-energy plaque radiation therapy) (11). Another development has been proton beam radiotherapy of iris melanomas, which avoids the cosmetic and functional problems of an extensive surgical iris coloboma and which provides better radiation dosimetry than brachytherapy. Follow-up has shown that most patients retain their pre-treatment visual acuity although many have required treatment for cataract and glaucoma. (Damato B, Kacperek A, Chopra M, Sheen MA, Campbell IR, Errington RD. Proton beam radiotherapy of iris melanoma. Int J Radiat Oncol Biol Phys 2005; 63: 109–115.) For patients with large tumors additional treatments are sometimes used after proton beam irradiation in order to improve globe preservation, final visual results and quality of life. Combined treatment modalitis, which can include radiotherapy + transpupillar thermotherapy, surgery, laser or intravitreal injection of anti-VEGF, are promising but need to be evaluated in a prospective way (8).

## Stereotactic Photon-beam Irradiation Therapy

Stereotactic radiation therapy (SRT) or radiosurgery stands out with favorable results during the last few decades (12, 13). This can be performed utilizing a gamma knife, a linear accelerator or a cyberknife. Re-

sults of the studies on fractionated SRT demonstrated that this technique is well tolerated and can be used in the treatment of uveal melanoma with good prognosis. These noninvasive techniques will probably increase their use in future (14, 15).

## Local Resection

Although surgical intraocular tumor resection techniques pose some difficulties and are technically challenging, they are effective alternative treatment options in selected cases of uveal tumors (16). The tumour can be removed en bloc through a scleral opening (i.e., 'exoresection') or in a piecemeal fashion with a vitreous cutter passed through the retina (i.e., 'endoresection') (17). Exoresection include iridectomy, iridocyclectomy, cyclochoroidectomy, and choroidectomy. Iridectomy results have improved with the development of artificial iris implants, pupilloplasty, and painted contact lenses. Iridocyclectomy techniques currently performed by the author have changed in the past decade. Previously, the pupil was dilated and the dissection was performed anteroposteriorly, commencing with a broad iridectomy. Today, the author constricts the pupil and excises the tumour in a postero-anterior or circumferential direction, conserving the iris sphincter and most of the iris in the affected sector, leaving only a small peripheral iridectomy. This improvement has resulted in a swing away from radiotherapy and back to surgical excision, which provides not only a cure but also tissue for diagnosis and prognostication. Endoresection can be performed through a retinotomy or under a large retinal flap. Phototherapy is also administered to destroy any tumour remnants in the sclera. (6) Both exoresection and endoresection can be under-taken as a primary procedure, or in combination with any form of radiotherapy, or after radiotherapy for recurrent or toxic tumour (18). Each of the treatment options has advantages and disadvantages, and thus optimal therapy is still controversial. As some authors point out, local resection preserves eyes that would otherwise be inoperable and produces relatively large tumour samples, which are useful for prognostication and research and which may one day have therapeutic value (17).

## Enucleation

Enucleation has been the primary treatment of choice for uveal melanoma and although it is not as prevalent as before, it still serves as a useful technique for the treatment of uveal melanoma. This surgical technique has improved in recent years: Castroviejo implants (which commonly extruded) are abandoned; administering a long-acting local anaesthetic with adrenaline, after general anaesthesia has been induced (to reduce intra-operative haemorrhage and post-operative pain) is now part of a surgical procedure; pressure bandage is applayed for 2 days, to prevent post-operative peri-ocular haematoma. Counselling patients about phantom eye symptoms, which are common and diverse, is also important (6, 19). Primary enucleation continues to be necessary in over a third of patients, because of late presentation, detection or referral (20). Although žno touch' techniques were popular in the past (21), modified techniques using a snare may avoid clamping of the optic nerve (22).

## Anti-angiogenic therapy

There is a broad experience with anti-angiogenic agents in patients with uveal melanoma by treating the complications of radiation therapy. Unfortunately, experimental and clinical trials using anti- VEGF monotherapy have been disappointing (23, 24).

## Immunotherapy

Novel therapies are being explored for their effectiveness against uveal melanoma metastases and immunotherapy may be a potential option as an alternative or adjunctive treatment, even in the prophylactic setting (25). The report at the American Association for Cancer Research (AACR) Annual Meeting 2015 in April, of results from a phase I/IIa clinical trial of a new type of immunotherapy — albeit in a small group of patients with advanced melanoma and ocular melanoma — is promising. The trial was of a first-in-class immunotherapy called IMCgp100, which is an affinity-enhanced T cell receptor (TCR) specific for the HLA-A2 restricted melanoma gp100 peptide (YLEPGPVTA) fused to an anti-CD3 antibody fragment. Due to its high affinity, IMCgp100 enables T cells to kill HLA down-regulated melanoma cells otherwise invisible to natural T cell recognition. IMCgp100 shows partial and complete durable responses in Phase I/IIa trial in patients with advanced melanoma. Importantly, two of the objective responses, one complete and one partial, were observed in the only two patients enrolled in the expansion cohort with ocular melanoma. This encouraging clinical activity suggests that ocular melanoma is an important subgroup of melanoma for IMCgp100 based on the high unmet need in this indication (26).

## Management of the metastatic disease

Over the years, several prognostic factors have been identified, which can distinguish patients at risk

for metastasis. Prognostic clinical and histological parameters include age at the time of diagnosis, tumor location, largest tumor diameter (LTD), the presence of epithelioid cells, a closed vascular loop pattern in the tumor and extra-scleral extension (27). Extensive research has been performed to identify genetic prognostic factors. Loss of chromosome 3 and gain of chromosome 8q as detected by FISH are associated with metastatic related death (28) whereas gain of the chromosomal region 6p correlates with a favorable prognosis.

Standard chemotherapy with an alkylating agent such as dacarbazine or fotemustine does not increase survival in patients who remain alive on average five to seven months (29). Since the nearly 90% of patients have only liver metastases, surgical treatments have been tried. Partial hepatectomy of isolated metastases would increase the survival of these patients, but only a small minority of metastases occur in this manner, most patients developing multiple deposits (29, 30). Studies on isolated liver perfusion with melphalan or TNF achieved significant prolongation of life, but the appearance of extrahepatic metastases was common and no benefit in survival was observed (31). Randomised clinical trial comparing intravenous chemotherapy to the hepatic arterial chemotherapy was peformed. The response rate is slightly increased in patients receiving intra-arterial chemotherapy but no increase in survival is observed (32). Newer agents are currently being investigated and these include ipilimumab and selective internal radiation therapy (SIRT) (26, 29). Genetic analysis of tumors provides us with valuable prognostic information although effective therapies are lacking at this moment. The current experience and new genetic techniques help to increase our understanding of uveal melanoma and discover pat-terns of growth and metastatic spread. This may result in precise identification of high-risk patients and targets for future adjuvant systemic treatments preventing metastatic disease (33).

## CONCLUSION

Progress in management of patients with uveal melanoma is significant due to improvement of pathology, ocular investigation, ocular treatment, prognostication, and treatment of metastatic disease. As a result of this progress, more long-term survivors with metastatic disease are being seen than ever before. It is not established yet whether prolonged survival is the result of treatment or whether it merely reflects earlier detection of metastases. Also, there are indications that 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 technique of gathering tumor tissue by fine-needle aspiration biopsy and new genetic techniques such as SNP-array and next generation sequencing will likely be crucial tools for improving diagnosis and therapy in the future. Further studies investigating the impact of ocular treatment on sur-vival should include only patients whose prognosis can be estimated according to the clinical stage, histological grade and genetic type. Therefore, the patients should be treated in experienced multi-disciplinary teams that must include these patients in clinical trial.

## Sažetak

# SAVREMENA TERAPIJA UVEALNOG MELANOMA

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Dijagnoza i terapija uvealnog melanoma pokazuju značajan progres poslednjih decenija. Uprkos tome, stopa preživljavanja pacijenata sa uvealnim melanomom se ne menja poslednjih pola veka. Modaliteti terapije uvealnog melanoma su: fototerapija, brahiterapija, protonsko zračenje, stereotaktična radioterapija, lokalna resekcija, antiangiogenetska terapija, imunoterapija i enukleacija. Genetska istraživanja tumora dala su značajne prognostičke rezultate, iako efektivne terapije još uvek nema. Još uvek je diskutabilno da li je duže preživljavanje rezultat terapije ili je posledica ranijeg otkrivanja metastaza. Takođe, postoje stavovi da preživljavanje posle tretmana uvealnog melanoma verovatno ne zavisi od vrste terapije već od mnogih kliničkih, histoloških i genetskih faktora rizika. Buduće studije o uticaju terapije na preživljavanje bi trebalo da uključuju pacijente čija se prognoza može proceniti prema kliničkom stadijumu, histološkom statusu i genetskom tipu tumora. Stoga, pacijenti bi trebalo da budu lečeni u referentnim multidisciplinarnim centrima, od strane iskusnih timova lekara koji mogu uključiti te pacijente u odgovarajuće kliničke studije.

***Ključne reči:*** Uvealni melanom, terapija, imunoterapija, metastatska bolest.

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