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Uveal melanoma – a review of treatment methods

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HIGHLIGHTS

Uveal melanoma is an aggressive tumor, which often metastasizes, therefore it is important to choose the appropriate and most effective treatment method for each patient.

ABSTRACT

Uveal melanoma is the most common primary intraocular malignancy. In Europe, the incidence of uveal melanoma is approximately 8 cases per million people per year. In about 50% of cases, uveal melanoma metastasizes. Scientific papers on uveal melanoma published between 1 January 2018 and 1 March 2023, available in the PubMed database were analyzed. Currently, methods such as enucleation, transpupillary thermotherapy, photodynamic therapy, eye plaque brachytherapy, proton beam therapy and stereotactic surgery are used to treat this cancer. In this paper we summarize the current knowledge about the classic treatment methods and the promising novel ones.

Key words: ocular melanoma, uveal melanoma, treatment methods

INTRODUCTION AND OBJECTIVE

Although uveal melanoma (UM) is an uncommon cancer, it is also the most prevalent primary malignancy of the eye in adults. Cancer can be located in various structures in the eye, but the choroid is still the most frequently affected one. Other affected parts of the eye are ciliary body and iris. Ciliary body melanomas have the worst prognosis, unlike iris melanomas, which are detected much earlier, resulting in a better prognosis [1]. Genetic and environmental factors that increase the risk of developing UM have been identified and they include fair skin color, dysplastic nevus syndrome, ocular melanocytosis and xeroderma pigmentosum. UM presents more often among male gender and Caucasian population. High estrogen levels may also be a risk factor because UM is more common during pregnancy. UM usually manifests in the sixth or seventh decade of life [2]. Nonetheless, the average age at which ocular melanoma is diagnosed differs between populations. UM is more common in carriers of *BAP1* or *BRCA1* mutations, but at the moment there is no detailed understanding of the pathogenesis [1].

UM typically develops as a result of an initiating mutation in the *G11/Q* pathway, which then activates a number of pathways, like *MAPK* and *YAP83*. In addition to the *GNAQ* or *GNA11* mutation, one of the following three mutations must also occur in the genes *BAP1, SF3B1,* or *EIF1AX* for a malignant transformation to happen. A tumor suppressor gene *BAP1* is found on chromosome 3, its loss occurs in about 35–45% of all UM and has the worst prognosis. Around 20–25% of UM cases are caused by a mutation in the gene *SF3B1*. Another 20–25% of tumors have *EIF1AX* mutations and typically they are the ones that have good prognosis [2].

The aim of our work is to present the currently used methods in the treatment of UM and the features that should be taken into account when selecting therapy for a particular patient.

Epidemiology

The incidence of UM in Europe is approximately 8 cases per 1,000,000 inhabitants per year [3]. The incidence and survival analysis of UM was conducted in Poland in 2010–2017. The study demonstrated that UM had an average incidence of 8.76 per 100,000 person-years and (the 1-year and 5-year OS rates were 91.61% and 60.76%, respectively). UM is metastatic in about 50% of cases, which is associated with an unfavorable prognosis [1]. The first line of treatment for choroidal melanoma includes radiotherapy, resection and enucleation. However, in about 50% of cases, this tumor metastasizes, which significantly worsens the prognosis. This, in turn, encourages us to work on finding more effective methods [1].

REVIEW METHODS

For the purpose of this study, a review of the English-language literature between 1.01.2018 and 1.03.2023 was performed in PubMed database. The following keywords were used to search the database: ocular melanoma, UM, treatment methods. A total of 41 studies were included in the review, all related to different methods of treatment for UM. Articles with no proven success rate on humans were excluded.

STATE OF KNOWLEDGE

Enucleation

Enucleation is a surgical procedure that involves complete removal of the eyeball, without affecting the oculomotor muscles or other contents of the orbit. Currently, it is considered the last remedy in treating UM and is performed only under some circumstances, which include large tumors, greater than 18 mm in basal diameter and with more than 12 mm thickness or taking up more than 40% of the eyeball's volume. Other indications are complete vision loss due to complications, neovascular glaucoma, optic nerve involvement and tumors recurrent to conservative methods [3, 4]. Thereupon, 35% of UMs are still treated by enucleation [5].

Proposing this radical surgery to patients often causes a lot of anxiety, due to the consequences. The obvious result of the procedure is loss of binocular stereoscopic vision, directly affecting everyday activities such as using stairs, walking in crowds and pouring drinks. Appearance concerns, irritation of tissues remaining in the orbit and phantom symptoms may also occur. Vision difficulties tend to decrease after 12 and 24 months, as patients develop adaptation strategies. The only outcome that seems to remain and increase is depression [5, 6]. Regarding effectiveness of enucleation, studies do not show any decrease in mortality compared to the non-invasive methods. However, it is difficult to judge independently, because patients that require this procedure usually already have a poor diagnosis, due to the size of tumors [7, 8]. In fact, there is one undeniable benefit of performing surgery instead of less invasive methods – the possibility of obtaining material for histopathological examination [9].

Other surgical methods are local resection and exenteration. A surgical option which spares the eyeball and is currently preferred over enucleation is local resection. It can be achieved either by endoresection or exoresection. In the first, the tumor is removed through the vitreoretinal approach and in the other – through the scleral approach [9]. Exenteration is a more intrusive procedure than enucleation. It involves the surgical removal of every tissue inside the orbit, including the eyelids. It is performed only in patients with tumors that are widely spread outside the orbit [9].

What worries clinicians is a very significant complication of surgical procedures – the risk of spreading cancer cells hematologically during the surgery [4]. Using radiation prior to those surgical procedures has been proven useless in metastasis prevention [8]. That is why for decades researchers have been working on alternative treatment that would allow the eyeball to be spared without the need for surgery and thus creating a better prospect of saving the vision in the affected eye. Once a gold standard in the treatment of UM, enucleation has now been majorly replaced by other, less invasive methods.

Currently, the commonly used forms of lasers in the treatment of choroidal melanoma are transpupillary thermotherapy (TTT) and photodynamic therapy (PDT). However, the use of these methods is limited to small posterior choroidal melanomas. These tumors should have well-defined margins with absent or minor retinal detachments. These procedures can be performed on an outpatient basis and should be classified as vision-saving methods. The end point to be achieved is a gray color of the tumor [10–12].

Transpupillary thermotherapy

Transpupillary thermotherapy as primary treatment is recommended for: low-risk small to medium-sized flat choroidal melanocytic lesions, undocumented tumor growth, patient leaning toward laser therapy, family history of UM, or patient's medical condition radiotherapy. TTT is used in recurrent marginal tumors and residual UMs. This method can also be used as a supplement to plaque radiotherapy and proton beam radiotherapy [11, 13].

TTT is a method that uses a near-infrared diode laser (810 nm), which is directed through the pupil at the neoplastic lesion. It is used to produce local temperatures in the range of 45–65°C. Laser beams that are used have a diameter of 2–3 mm and the exposure time is maximum 1 minute. This results in tissue necrosis even to a depth of 3.9 mm. The applied laser power depends on the pigmentation of the tumor. The laser beam is initially aimed at the top of the tumor, then the laser energy is adjusted so as to obtain a gray coloration of the tumor. Then the laser is directed to the entire surface of the tumor with 1.5 mm margins. The procedure should be repeated every 4 weeks until the tumor is clinically inactivated [11].

Adverse effects of the method include retinal detachment and traction, vitreous haemorrhage, iris neovascularization, cystoid macular edema, branch retinal vein occlusion, branch retinal artery occlusion, retrobulbar tumor extension and scleral infiltration [11].

Studies have shown that the use of the TTT laser is associated with an approximately 20.8% risk of recurrence from 10 months to 12.5 years. For this reason, the "sandwich therapy" (ST) was invented, which consists of the combination of TTT and ionizing radiation. This therapy allows to reduce the recurrence tumor and the radiation dose, which reduce the complications of brachytherapy with ^{125}I [11].

Photodynamic therapy

A method that is used in the treatment of posterior choroidal melanoma is photodynamic therapy. It is usually limited to smaller tumors because the total area of larger tumors is more difficult to visualize. Also, in thicker tumors laser penetration may be difficult and reduce the effectiveness of the method. It is important that the lesions are minimal or unpigmented [13].

This method is based on the intravenous administration of a photosensitizing agent – verteporphyrin. The photosensitizer accumulates in the abnormal blood vessels of the retina and choroid, which after 5 minutes are irradiated with the light of a non-thermal transpupillary laser with a length of 690 nm. This results in the release of free radicals, leading to apoptosis or vascular closure (necrosis). This is due to a secondary immune response. The effect depends on cell type, concentration and intracellular location of verteporfin and oxygen level. The procedure is repeated on an outpatient basis every 6 weeks, until the tumor is clinically inactivated [11].

Tumors are characterized by hypoxia and high oxygen consumption, which may adversely affect the effectiveness of the method, because of the important role of the oxygen radicals. Another component affecting efficacy is tumor perfusion, which connects with verteporphyrin distribution [11].

Complications of PDT are tumor recurrence, failure of local treatment, retinal traction, vitreous haemorrhage, chorioretinal neovascularization, scleromalacia, extradural tumor extension, and retinal vein branch occlusion [11].

Eye plaque brachytherapy

Eye plaque brachytherapy (EPBT) is a widely used eye-preserving method in UM treatment. Plaques with sealed radiation sources are sutured to the sclera within or next to a target. Some authors suggest that confirmation of plaque placement with intraoperative ultrasound can be favorable and even reduce the local recurrence of the tumor [14].

To obtain effective local control, The American Brachytherapy Society (ABS) consensus guidelines defined proper plaque placement as comprising safety margin which typically measures up to 2–3 mm. Taking this into consideration, UMs localized peripapillary, juxtapapillary or circumpapillary can be a challenge due to the width of the optic nerve sheath (5–6 mm) possibly resulting in inadequate tumor coverage. In one retrospective study it was claimed that brachytherapy of UMs near or touching the optic disc poses a high risk of treatment failure. ^{106}Ru and ^{125}I notched and non-notched plaques were discussed in that paper [15]. On the other hand, a 12-year study with

UMs treated with slotted ^{103}Pd plaques presented satisfactory local tumor control with few SE [16].
The surgery when the plaque is placed or removed should be performed under general or regional anesthesia. Duration of treatment may vary and typically range between 5–7 days. However, EPBT for small tumors treated with ^{106}Ru can last about 3 days [17].
Although some studies showed that EPBT may be beneficial for large UMs, it is usually applied for small- or medium-sized ones (< 18 mm in diameter, < 2.5 mm in height and < 18 mm in diameter, 2.5–10 mm in height respectively) [8].
Commonly used radioisotopes in plaque seeds include ^{125}I and ^{103}Pd which emit low-energy gamma rays, and ^{106}Ru which emits β rays and has 3 times quicker dose fall-off than iodine. Due to its characteristic, and thus lower depth of penetration, ^{106}Ru plaques are typically used for tumors with apical height < 6–7 mm [18]. According to ABS consensus guidelines, radiation doses to the tumor apex range from 70–100 Gy. However, it was suggested that dose adjustment and using lower doses of radiation within the clinical range may be beneficial for patients with no significant increase in hazards of UM-related mortality [19, 20].
EPBT is an effective treatment of UM and enables the globe preservation in cases that would have required enucleation in the past. In the *Collaborative Ocular Melanoma Study* (COMS), it was reported that there weren't any clinically or statistically significant survival differences between patients with medium-sized choroidal melanomas treated with ^{125}I EPBT and those treated with enucleation [21]. There are a few factors that can affect the outcomes. A retrospective study showed that the largest basal diameter and the initial tumor height were predictors of tumor regression, whereas the largest basal diameter was associated with metastases. The COMS indicated that older age and the largest basal diameter were the main predictors of time to death from all causes and death with melanoma metastasis [22, 23]. A meta-analysis evaluating possible side effects of ^{106}Ru EPBT treatment showed that vision-threating complications such as retinopathy and cataract may occur. Optic neuropathy and ocular hypertension were also mentioned. It was reported that EPBT with accompanying procedures can affect ocular muscle functions, sclera integrity and ocular surface [24, 25]. In one retrospective study involving 350 patients (350 eyes) with small and medium UM (with a maximum of 6.5 mm in apical height), tumors were treated with ^{106}Ru EPBT with a total dose of 100 Gy to the tumor apex. Complications 5 years after treatment manifested as radiation maculopathy (135 patients, 38%), optic neuropathy (40 patients, 11%) and cataract (50 patients, 14%) [26]. Additionally, a single centered study with ^{106}Ru EPBT reported local recurrence and neovascular glaucoma as main reasons for secondary enucleation (SE). However, the enucleation rate after 10 years was lower than in other studies mentioned in that paper (6,3% vs. 18% and 19,2%). Similarly, in research with patients treated with ^{125}I plaques the leading causes of SE were the same except for SE rate (15%) [27, 28].
In a comparative study assessing patients with tumors ≤ 5 mm in apical height, cataract and radiation retinopathy were significantly more common in ^{125}I than in ^{106}Ru EPBT. In this retrospective review no patient treated with ^{106}Ru plaques had to undergo SE [29]. A study involving patients with ≥ 5.5 mm thick tumors only reported significant difference in repeated brachytherapy rate which was higher among group treated with ruthenium plaques [18].

Proton beam therapy

Besides plaque brachytherapy, proton beam is also a very common treatment method of UM, which uses charged particles to distribute a specific, localized radiation dose to the tumor [30]. The particles radiate most of their energy at a certain depth – Bragg peak causing less damage to the surrounding tissues [4]. The most commonly used ones are protons and helium ions [13]. A radiation dose of 50–70 cobalt Grey equivalent is usually delivered in 4–5 fractions [3, 9, 13]. During the sessions, the head is positioned by face mask and dental bite block [3, 13]. Specifically directed to large tumors, located closer to fovea or optic disk [31, 32]. Moreover, in lesions up to 16 mm in diameter it is considered to be the most efficient. PBR not only can be used as a primary treatment, but also in therapy of recurrent tumors, before surgical resections and after surgeries as an additional therapy [31]. Despite many great advantages, proton beam therapy can also cause damage to ocular structures [9]. Adverse outcomes of proton beam include cataract formation and neovascular glaucoma, maculopathy, vitreous hemorrhage and papillopathy [9, 31]. One study examined 306 patients with UM, who were managed with stereotactic radiosurgery (SRS) (n = 153) or PBR (n = 153). Vitreous hemorrhage was a more common side effect in SFR patients. On the other hand, optic neuropathy and maculopathy were more likely to occur in PBR patients [33]. According to a different study, there are lower chances of secondary enucleation compared to stereotactic radiotherapy [25]. Another study evaluated quality of life after PBR in comparison to enucleation and showed a high risk of reading difficulties and visual impairment. Particularly there were incidents of central and peripheral visual loss and visual sensation [5]. A different study demonstrated that quality of life after PBR was diminished among female patients versus male patients. Additionally, 3 months after PBR, patients reported symptoms more specific to the eye [34]. The COMS performed a survival analysis of cases managed with PBR and brachytherapy. No difference between the 2 methods was reported [2]. Local recurrence of tumor cells was 3.5% at 5 years and 5% at 10 years [4].

There are a few disadvantages including the requirement of general anesthesia. It is problematic because of the middle age of onset of UM. In addition, the cost is substantial [25]. Radiation keratopathy, which can occur after PBR in up to 12% of cases, is another problem. Decreased corneal sensitivity may be the first symptom. Apart from that, other conditions including dry eye disease, scleral necrosis, and pseudophakic bullous keratopathy can also happen [35]. A cohort study in 424 patients with small UM (T1) treated by PBR noticed good tumor control and long-term visual outcomes for tumors located ≥ 3 mm from fovea-optic disc and a risk of poor vision for those located closer than 3 mm. They concluded that the location of the tumor influences the risk of vision loss [30]. In another study, patient-reported outcomes and quality of life after UM treatment were assessed. They included 442 patients after enucleation, 730 after plaque brachytherapy and 424 after proton beam therapy. Radiotherapy was related with more concern about local recurrence. Furthermore, diplopia and headache were more frequently reported, and visual difficulties appeared over time [6].

Stereotactic surgery

An improved technique of external beam radiotherapy, which includes gamma knife therapy and cyber knife therapy is SRS. As in PBR, the charged particles are used to deliver a dose of ionizing radiation to a well-circumscribed target volume. The head has to be immobilized in gamma knife therapy, whereas in cyberknife therapy there is no need for that [25, 36]. Complications, such as radiation retinopathy and neovascular glaucoma, were reported more frequently after SRS, than PBR or plaque brachytherapy. In some series, secondary glaucoma appears in almost half of the cases. SRS is often used when plaque brachytherapy is considered inappropriate due to large, peripapillary or posteriorly located tumors [4]. A meta-analysis conducted on 1000 UM cases treated with SRS noted a 5-year survival rate of 76% and effectiveness in tumor control in 96% [3]. However, other possible side effects that might be observed in UM patients treated with gamma knife are blepharitis (16%) and long-lasting corneal epithelial (15%). The second one is especially important, given the fact that it occurred in the first 3 months after starting therapy. Another study of 158 UM patients reported blepharoconjunctivitis, corneal epithelial defects, epitheliolysis, and madarosis. Prevalence ranges from 3% to 6%. Moreover, these complications occurred more frequently when the tumor was close to the anterior segment of the eye [35]. In another study, gamma knife therapy was used in UM patients. They noted higher ocular morbidity in the lesions thicker than 8 mm and that doses larger than 10 Gy/fraction were related with higher probability of radiation-induced inflammatory. Compared to PBR, which is used to treat small- and medium-size lesions, both efficacy and side-effects were similar. When taking into consideration these 2 methods, SRS is minimally invasive and less expensive to operate than PBR [31]. To summarize, authors present suggestions for choosing the right treatment for the UM in table 1.

TABLE 1

Choice of method in UM treatment based on tumor features.

Method	Tumor features	
	Size	Others
Exenteration	-	spread outside of the orbit
Enucleation	> 18 mm	> 12 mm in height, taking up more than 40% of the eyeball's volume, optic nerve involvement
Eye plaque brachytherapy	< 18 mm	< 10 mm in height
Proton beam therapy	< 16 mm	located closer to fovea or optic disk
Photodynamic therapy	-	minimal or unpigmented lesions
Stereotactic surgery	-	peripapillary or posteriorly located tumors
Thermotherapy	-	undocumented growth, as a supplement to plaque radiotherapy and proton beam radiotherapy

Novel treatment methods

The urgent need to find a better solution for patients with UM led to extensive research into possible use of the latest technologies in treatment, some of which showed very promising results.

The immunological treatment has been proven greatly successful for many types of cancer. It is currently a very exciting area of drug development. The Immune Checkpoint Blockades (ICB) are anti-PD-1-antibodies (nivolumab, pembrolizumab), anti-CTLA-4 antibodies (ipilimumab, tremelimumab), anti-PD-L1 antibodies and PD-1 inhibitors [37]. They have been tested in UM treatment for years now, yet the individual studies results weren't spectacular. However, newer studies suggest different conclusions. Meta-analysis conducted in 2021, analyzed 16 full-text articles about ICB. This study demonstrated that ICB therapy was effective in treating UM, with an increased long-term survival and a good safety profile. Additionally, the ICB treatment caused a decrease in adverse and serious adverse events [37]. Another perspective of immunotherapy is using an IMCgp100 bio specific molecule. Two studies presented in 2017 showed significant disease stabilization and an increase to 73% in 1-year overall survival (in both studies) [38].

The CAR-T therapy has proven to be a groundbreaking method in oncology. Data from 2019 indicate that the UM can respond to HER2 CAR-T cells. Both in vitro and in vivo

studies demonstrate that the method is effective in killing the UM cancer cells in a target-specific way. Not enough studies have been conducted to affirm safety and long-term outcomes of CAR-T in UM, yet it is certainly a very promising perspective [39].

An optimistic study came out in 2021, depicting the effects of a self-assembling nanofiber hydrogel containing a gene-targeted drug. The hydrogel strengthened the eyeball, whereas the low-density near-infrared (NIR) light induced photothermal transition and gel-sol alteration. This method presented excellent antitumor efficiency in vitro and in vivo. In addition, the influence on healthy cells was minimal, which confirms the safety of intraocular tissue. Hence, the developed CP@Au@DC_AC50 emerges as a viable approach for UM therapy using one injection [40].

Nanoparticle therapy is a very specific treatment that creates an immense possibility of preserving the sight. Due to its selectiveness, it could be especially useful to patients with poorly located tumors, such as in proximity to the optic nerve. A study conducted on 12 patients suggests that this method could prove to be useful in the future [2].

Another study in this area, performed in situ with curcumin-loaded polymeric nanoparticles, found great results in inhibiting proliferating cancer cells [41].

An alternative study on human cells, conducted in 2020, tested cinobufagin secreted by the Asiatic toad Bufo gargarizans. The study suggests that it could potentially be effective in inducing UM cancer cells apoptosis, simultaneously inhibiting cell survival [42].

A significant part in the malignancy of UM is played by the dysregulation of the ubiquitin-proteasome (UPS) system. The UPS-targeted therapies are also promising therapeutic strategies against UM. They could also be considered a foothold for the future of UM [43].

Naturally, more clinical research is needed in all of the above, nonetheless these emerging methods certainly create hope for the future of patients with UM.

CONCLUSION

UM is the most common intraocular malignancy. Currently, methods such as enucleation, transpupillary thermotherapy, photodynamic therapy, eye plaque brachytherapy, proton beam therapy and stereotactic surgery are used to treat this cancer. Small and medium-sized melanomas can be treated with transpupillary thermotherapy, proton beam therapy and brachytherapy. Large melanomas can be treated with proton beam therapy or may require more extensive surgery. The most common method remains radiation, although this could change, due to extensive research on the treatment of UM. In addition, research is being conducted on new treatments. New methods include: immunotherapy, CAR-T cells, nanoparticle, cinobufagin, the ubiquitin-proteasome system and self-assembling nanofiber hydrogel containing a gene-targeted drug. Research into new methods is important because choroidal melanoma metastasizes in about 50% of cases.

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