Review

Radiation treatment methods in uveal melanoma

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ABSTRACT

Background: The most frequent primary ocular malignancy in the western world is the uveal melanoma. While it mainly affects Caucasians, it is extremely uncommon among non-Caucasians. Continuous improvement in therapies for local treatment has allowed sparing of the eye, although this approach apparently does not improve survival. The present review aimed to explain different radiotherapy (RT) methods and compare the pros and cons of each method, along with the main complications that may be encountered in the treatment of uveal melanoma.

Methods: Relevant papers published between September 2009 and January 2021 were retrieved, reviewed, and screened. Four databases, including PubMed, MEDLINE, Google Scholar, and GeneCards, were searched for this purpose.

Results: Forty-one relevant articles were identified. Based on the selected papers, we highlighted the advantages and disadvantages of the different RT methods that have allowed sparing of the eye, even though they have not, as yet, improved survival. We listed a detailed comparison between therapies that allow an educated choice among the different available RT methods.

Conclusion: The choice of uveal melanoma management is determined by the location of the tumor and volume of the extraocular extent. At present, there is no gold standard for the management of all ocular melanomas, and each case should be approached individually. Therefore, classification is a valuable prognostic tool. Many cases in cT3-4 classification categories are treated by primary enucleation and conservative treatment follow-up, while in cT2 and most cT1 classifications (i.e., 3.1–6.0-mm tumor thickness), several forms of RT are used.

KEY WORDS

melanoma of the uvea, choroidal melanoma, radiation therapy, brachytherapy, radioisotope brachytherapy, proton beam therapy, classification

INTRODUCTION

Melanoma is a malignant tumor associated with melanocytes, rarely associated with the eyes and tissues surrounding the eye (5%), even rarer is melanoma of mucosal origin (1%). An additional 2.2% of melanomas have unknown primary sites [1-3]. The uvea (85%), eyelid/orbit (10%), and conjunctiva (5%) are the most frequent tissues in which ophthalmic melanomas arise [2, 4, 5].

Uveal melanoma (UM) is the most common primary ocular malignancy [4, 6-11]. The incidence of UM in the western world is approximately 6 per million population per year [12]. The worldwide occurrence is estimated to

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How to cite this article: Tsotridou E, Loukovitis E, Tsiropoulos GN, Zapsalis K, Pentara I, Tzima K, Eminidou V, Anogeianakis G. Radiation treatment methods in uveal melanoma. Med Hypothesis Discov Innov Ophthalmol. 2021 Spring; 10(1): 32-42. https://doi.org/10.51329/mehdiophthal1419

be between 4 and 7 cases per million people per year [4, 6, 7, 11, 13-20]. It primarily affects Caucasians, whereas it is very uncommon among non-Caucasians [17, 21]. UM most commonly affects adults aged 50–80 years, without a sex bias. It is predominantly unilateral [17] with bilateral choroidal melanomas (CMs) occurring in only 1 in every 50 million Caucasians [19].

The incidence of UM is estimated to be 1.3-8.6 cases/million people, and CM is the most frequent primary intraocular malignancy in the western world [22, 23]. In contrast, it is approximately 20 times less frequent in Asia, where the reported incidence is about 0.25 cases/million individuals/year [22]. African American and Hispanic populations are less prone to developing UM than Europeans, while Chinese individuals are apparently affected at younger ages than westerners [13]. In Europe, the incidence of malignant UM is estimated to be 3-5 cases/100,000 individuals/year in Mediterranean countries [18, 24].

Individuals with congenital ocular or oculodermal melanocytosis (nevus of Ota) and uveal nevus are predisposed to melanomas, and particularly CM. In addition, somatic mutations in *GNAQ*, *PTEN*, and *GNA11* are found in > 50% of CM patients [20]. The continuous improvement of local treatments has allowed sparing of the eye, although this approach apparently does not improve survival. The present review aimed to compare the pros and cons of different radiotherapy (RT) methods, as well as the main complications that can be encountered in their application in the treatment of OM.

METHODS

Relevant papers , published between September 2009 and January 2021, were retrieved by searching the PubMed, MEDLINE, Google Scholar, and GeneCards databases. "Melanoma," "radiation therapy," "brachytherapy," "choroidal melanoma," "proton beam therapy," and "classification" were the keyword combinations used. The identified papers were screened and appropriate papers were selected for inclusion in the review.

RESULTS

Forty-one articles compatible with the aim of the current review were selected, and we focused on the most recent publications. Based on the 41 reviewed papers, we highlighted the advantages and disadvantages of the different RTs that have allowed sparing of the eye, even though they have not, as yet, improved survival in patients with OM. Table 1 lists the studies included in the present review, highlighting the key findings of each study. A summary of the main RTs used in the last decade for the management of UM is presented. Several factors were considered for the selection of the appropriate method, including tumor size, histopathological and genetic characteristics, tumor location (particularly when it is anterior), and presentation with extraocular extension (EOE) at the first examination [25]. We compiled a detailed comparison between therapies that allow an educated choice among the different available RT methods**.** In addition, Table 2 refers to the main RTs reported in the text and focuses on the advantages, disadvantages, and complications that are triggered by each method.

Table 1. Details of studies included in the current review

Author (Year of Publication)	Type of Study	Key findings
Romanowska-Dixon et al. (2012) [1]	Cross-sectional study	Following PBT, tumor thickness was 3.17 mm (1.5-9.3 mm). PBT achieves local control in high rates.
Dunavoelgyi et al. (2013) [2]	Cohort study (prospective observational)	Hypofractionated SRT achieved high efficiency in CMs when used at a dose of 50 Gy in 5 fractions.
Kawczyk-Krupka et al. (2013) [3]	Review	PDT may be a promising management, as many studies report the regression of cutaneous and CM.
Al-Wassia et al. (2011) [4]	Retrospective case series	SRT using 60 Gy in 10 fractions is an effective and safe management.
Verma et al. (2016) [5]	Systematic review	PBT appears effective as it preserves visual acuity and provide high survival outcomes
Dunavoelgyi et al. (2011) [6]	Cohort study (prospective observational)	SRT achieves effective local tumor control and has comparable results to PBT.
Macdonald et al. (2011) [7]	Retrospective case series	PBT is a suitable eye-preserving melanoma management used mainly in medium and large UMs.
Reynolds et al. (2016) [8]	Letter to the editor	Carbon fiducials for assistance with Gamma Knife radiosurgery treatment may be helpful when UM cannot be visualized on magnetic resonance imaging.
Somani et al. (2009) [9]	Retrospective case series	SRT is a noninvasive alternative treatment for CM, with acceptable rates of ocular toxicity.
Haji Mohd Yasin et al. (2016) [10]	Retrospective study	SRT provides local control and eye retention. Intravitreal injection of bevacizumab seems not to decrease the rate of radiation retinopathy.
Bensoussan et al. (2016) [11]	Retrospective, consecutive cohort study	PBT results in high rates of local control, without deterioration of survival. It may be used as an alternative approach in large CMs.

Jager et al. (2020) [12]	Review	The understanding of tumor immunology and metabolism may lead to better control and achieve new, more effective treatments.
Tsai et al. (2018) [13]	Case report	GK-SRS can be utilized as a brief single-fraction treatment.
De Caluwé et al. (2018) [14]	Retrospective study	A D_{min} of 65 Gy in the management of the CM is needed to achieve a response.
Mitsch et al. (2018) [15]	Original article	The regression rate appears to be non-linear , in contrast to very rapid or slow early tumor responses after treatment of CM with LINAC SFRT.
Fabian et al. (2018) [16]	Retrospective analysis	After treatment with 3 sessions of PDT, 62% of cases with posterior pole cT1a CM showed tumor regression in 27 months. Better response was reported in cases with ≤ 3 risk factors.
Rundle (2017) [17]	Review	The use of PDT remains controversial in ocular oncology. However, with appropriate case selection it may provide acceptable local control rates and visual acuity.
Mosci et al. (2014) [18]	Original article	In the post-PBT follow-up of UM, internal reflectivity seems to be a better indicator of early response when it is used in large tumors.
Mustafi et al. (2017) [19]	Case report	It is important to monitor patients with CM, particularly when choroidal nevi are present.
Sas-Korczyńska et al. (2014) [20]	Original article	PBT achieves good results when used in CM. The rate of eye preservation was 93% and vision was protected in 80% of patients.
Weber et al. (2015) [21]	Cohort study (prospective observational)	PBT provides acceptable survival rates and tumor control when used in large and anteriorly located melanomas. Vision function was acceptable and toxicity rates requiring enucleation were low.
Kim et al. (2018) [22]	Retrospective analysis	The results of PBT for CM were comparable with previous reports. Significant volume regression was reported after PBT.
Tran et al. (2012) [23]	Retrospective analysis	Excellent local control and toxicity rates were reported after PBT. T3 tumors appear to have higher rates of metastases and recurrence.
Virgili et al. (2007) [24]	Incidence analysis/ case-control study	The incidence rate of UMs between 1983 and 1994 was reported to be stable.
Seibel et al. (2018) [25]	Retrospective case series	PBT appears to present acceptable results when used in extraocular extension melanoma.
Gianniou et al. (2017) [26]	Case report	Calcified UM should be included in the differential diagnosis of cases with an atypical calcified and non-pigmented mass.
Fabian et al. (2017) [27]	Prospective analysis	PDT is an efficient treatment with a tumor control rate of 80%.
Schonfeld et al. (2014) [28]	Retrospective analysis	PBT provides efficient management in mid-zone CMs. However, consecutive treatment is frequently required.
Turkoglu et al. (2019) [29]	Retrospective analysis	PDT as a primary treatment achieved complete regression of the small amelanotic CM over 5 years in 67% of cases.
Sellam et al. (2017) [30]	Retrospective case-control study	Using optical coherence tomography angiography in patients with CM who were treated with PBT, both inner and outer plexus layers of choroid revealed changes, along with vascular rarefaction of the choriocapillaries.
Krema et al. (2009) [31]	Retrospective case series	SRT shows high efficacy, but enhances long-term ocular complications.
Chojniak et al. (2011) [32]	Prospective nonrandomized study	TTT is effective for the management of CM. However, subfoveal and perifoveal tumors show an early decrease in visual acuity.
Hartsell et al. (2016) [33]	Prospective study	High local control rates and low enucleation risk rates were reported using 3D treatment planning for proton therapy of CMs.
Riechardt et al. (2014) [34]	Clinical case series, retrospective study	Radiation-induced optic neuropathy may be present in several cases, but useful vision may be preserved at an acceptable rate.
Phillips et al. (2013) [35]	Retrospective case series	A 3D conformal radiotherapy technique was efficient in the management of CM.
Russo et al. (2015) [36]	Prospective case series	Ultrasound and particularly magnetic resonance imaging could be used in the follow-up after PBT.
Campbell et al. (2012) [37]	Case series	Short-term efficacy of PDT for amelanotic CM is high, without vision impairments, although the long-term effectiveness is uncertain.
Yan et al. (2018) [38]	Research article	A novel focused kV X-ray technique with potential NP protects healthy tissues while providing flexibility for management planning in patients with ocular melanoma.
Dunavoelgyi et al. (2012) [39]	Retrospective study	Hypofractionated SRT and PBT present comparable rates of long-term side effects (low to moderate) when used for central CM.
Konstantinidis et al. (2015) [40]	Retrospective study	PBT avoids upper eyelid margin damage and complications. Additionally, local tumor control remains stable.
Konstantinidis et al. (2014) [41]	Non-randomised, prospective case series	Toxic tumor syndrome (the persistence of the irradiated eye tumor within the eye) after PBT of a CM provokes complications, such as neovascular glaucoma and exudative retinal detachment.

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; UM, uveal melanoma; CM, choroidal melanoma; D_{min}, minimum dose to the tumor; GK-SRS, Gamma Knife Perfexion® stereotactic radiosurgery; kV, kilovolt; LINAC, linear accelerator; NP, nanoparticle; PBT, Proton beam radiotherapy; SFRT, stereotactic fractionated radiotherapy; SRT, stereotactic radiotherapy; PDT, photodynamic therapy; TTT, transpupillary thermotherapy.

Table 2. Evidence based advantages, disadvantages, and complications of the main RTs

Radiation Therapy	Advantages	Disadvantages/Complications
RT Modalities	Privileged treatment in medium-sized and symptomatic, small CMs [35]. RT uses X-rays, whereby high-kinetic energy electrons are directed at deep seated tumors [38]. A focused kV beam X-ray technique causes significantly less damage in critical structures of the eye than PB, costs less, and does not involve surgery [38].	X-rays used are non-directional and not focusable. Thus, RT lacks precision and therefore puts organs (non-targeted but near the tumor) at risk of being damaged, even if synchrotron-based beams are used [38]. Poor visual outcomes in juxtapupillary lesions [4].
External Beam Therapy	In the case of UM, proton and helium-ion RT achieve > 90% local tumor control [6].	In 5% of cases, recurrent tumor growth was detected with a median follow-up of 53.2 months. Among 39 enucleated eyes, the 2 most common causes of enucleation were NVG and recurrent tumor growth, in 25 and 8 cases, respectively [6].
CPT	Promising results have been reported in the treatment of juxtapupillary tumors [14, 35]. Low local failure rates have been reported (4.21%); SRT had rates of 6.20% and PB 9.45% [10].	CPT has the drawback of greater neutron tissue exposure, as compared with essentially no exposure when using photons [14, 35].
PBT	PBT is applicable in a wider range of tumors (both posterior peripapillary tumors and anteriorly located tumors) [4, 20, 21, 23, 33, 40]. Twenty percent of ocular melanomas are treated with PBT [20]. Local control rates of over 90%, sustained for 10 years [5, 20, 23] were achieved. It is suitable for cases where brachytherapy is not advised, including large tumors or cases with extrascleral extension [21]. It reduces metastasis rates [11] and the potential need for enucleation as compared with brachytherapy [20]. It is superior in maintaining healthy tissue [2] and has good eye retention rates [11].	It offers a low visual acuity prognosis and rate of eye conservation for large melanomas [2]. It has more anterior segment complications [11]. Irradiating large volumes with exceedingly high doses increase complications rates, resulting in secondary enucleation [7, 11]. Although most tumors shrink, they do not disappear after irradiation [18]. The ocular recurrence-free rate for nonperipapillary melanoma is approximately 85% at 5-years, which is lower than the 90–97% rate for medium-sized tumors [21]. Complications: retinopathies (23-67%), cataract (20-62%), glaucoma (7-30%), optic neuropathy (7-33%), and vitreous bleeding (9-14%) [5]. Rubeosis iridis and NVG after PBT may lead to enucleation [7, 22, 28]. Microvasculopathy may ensue [30].
SRT	Management of juxtapapillary CM by delivering an adequate dose, independently of tumor location in relation to the optic disc [35, 39]. Noninvasive methods, such as MRI and CT, can determine the tumor's location and borders [2, 31]. No preoperative surgical marking is necessary. SRT is more cost-effective [2]. It seems to be superior to GK radiosurgery because it utilizes a relocatable immobilization frame and thus delivers irradiation in multiple fractions [6]. Surgical insertion of localization clips in melanomas patients seems to be another SRT advantage [22]. The SRT tumor control rate has been reported as 94% at 37 months, which is comparable with the 85% 5-year rate for brachytherapy of juxtapapillary melanoma or the 83% rate for helium-ion RT [31].	The delineation of the extent (borders) of the tumor based only on CT images is challenging [22]. Radiation retinopathy may ensue [10].
GK Radiosurgery	GK irradiation employs a fixed immobilization frame that is anchored to the skull to ensure akinesia during the single-dose radiosurgery [6, 31].	It seems to be inferior to SRT [6, 31].
PB	PB apparently provides equivalent survival rates to PBT [7, 20]. It is less expensive and time-consuming than PBT [20]. It is the preferred eyeball-preserving treatment for CM [22].	Local control of posterior tumors by PB is inferior to that achieved with PBT. This is attributed to imprecise position of the plaque (particularly at the posterior pole) and suboptimal immobilization of the plaque [5, 11].
TTT	TTT, compared with plaque radiotherapy, results in rapid tumor regression. TTT has less severe and diffuse side-effects and complications. It is effective in selected small CMs [32].	Visual acuity is reduced, and is detected early after treatment or mainly concomitant with treatment, and complications of subfoveal and perifoveal tumors. Complications, in order of frequency, are retinal vascular occlusion, papillopathy, retinal traction, retinal detachment, vitreous hemorrhage, and maculopathy [32].
PDT	Good tumor control rates in pigmented and non-pigmented CMs [16].	High recurrence rate, even in small CMs [16].

Abbreviations: CM, choroidal melanoma; CPT, charged particle treatment; CT, computed tomography; GK, Gamma Knife; kV, kilovolt; MRI, magnetic resonance imaging; NP, nanoparticles; NVG, neovascular glaucoma; PB, plaque brachytherapy; PBT, proton beam therapy; PDT, photodynamic therapy; RT, radiotherapy; SRT, stereotactic radiotherapy; TTT, transpupillary thermotherapy; UM, uveal melanoma.

DISCUSSION

Melanoma mostly metastasizes either by local spreading or by hematogenic dissemination [7, 10] with between 2.3% and 5.5% of the patients presenting with EOE at the first examination. Poor survival is associated with larger tumors and anterior tumor extension, diffuse melanoma, and genetic and histopathologic characteristics, such as epithelioid cell type, which are also associated with EOE [25]. Almost 50% of patients show simultaneous metastasis at the initial diagnosis [15], which is responsible for the death of nearly 50% of UM cases [17]. The principal site of metastasis is the liver [2].

The location and volume of the EOE determine the choice of treatment. Most patients present with anterior EOE. When EOE appears posteriorly, enucleation is the most frequently used technique. Therefore, there are fewer than 50 reports in the literature regarding the implementation of primary irradiation in patients with posterior EOE. In these cases, local recurrence rates are reported to be equally low, irrespective of whether plaque radiotherapy (PR) or proton beam therapy (PBT) are used for treatment [25]. It is important to note that EOE is not associated with loss of local tumor control, and it is not a marginal factor in local failure of PBT. However, EOE with a tumor diameter > 5 mm is associated with loss of local tumor control and is a marginal factor in local failure of PBT. It is also an additional risk factor for metastasis and vortex vein invasion. Optic nerve infiltration occurs in 5.7% of UM cases. However, optic nerve invasion is reported to occur in approximately 34% of patients with no funduscopically identifiable juxtapapillary tumor growth [25, 26].

Depending on the irradiation modality used for treatment, the outcome depends on tumor size, plaque size, radiation dose, and the amount of tissue damaged by radiation [27]. Visual prognosis also depends on the tumor position relative to the fovea and optic disc [22]. The introduction of better therapies, which have been successful in local treatment during the last 3 decades, has allowed sparing of the eye in many cases, although it is debatable whether they have improved survival [2].

Given that the prognosis of metastatic disease is poor [7, 10], decisions regarding small tumors should be based on the presence of indications of malignant transformation and the inherent risks of treatment [2]. The most notable predictive factors for melanoma-associated mortality are the associated genetic alterations [15], while age, initial tumor dimensions, tumor location, and epithelioid cell type are risk factors for metastasis [2, 15, 23]. Tumor diameter at presentation (> 10 mm), male sex, and age (> 60 years) are the most reliable predictive factors for metastatic disease [28]. Perimacular and peripapillary melanomas have a higher risk of local recurrence [6]. The 5-year survival rate of UM is estimated to be between 69% and 82% [10]. Tumors anterior to the equator that invade the ciliary body have a very poor prognosis. Tumors posterior to the equator that invade the optic nerve or the macula region exhibit a better prognosis. Tumors of the anterior aspects of the eye may be difficult to detect and may be asymptomatic and often present at more advanced stages [21].

UMs are classified by the American Joint Committee on Cancer (AJCC) based on a number of variables, including tumor size, tumor localization, and whether or not they present with EOE. The AJCC classification is a valuable prognostic tool. CM, classified by the AJCC as *c*T3-4, is treated by primary enucleation with conservative treatments, with variable results. For *c*T2 and *c*T1 classifications (i.e., 3.1–6.0-mm tumor thickness), local RT, PR, or PBT are used. For *c*T1a tumors, which present with thickness ≤ 3 mm, or those cases that may be characterized as "borderline" (i.e., suspicious nevi), opinions differ. Many investigators have proposed early treatment of these tumors with local RT, with the aim of reducing the possibility of adverse mutations and lowering the metastatic risk. Others prefer not to treat small lesions in asymptomatic patients, provided that there is no evident tumor growth, to avoid the deterioration of vision that is the result of RT in > 50% of cases [16]. There is no universal agreement on the optimal treatment option for patients presenting with T3 tumors; however, cautious investigators suggest that the upfront enucleation option must be followed. There are a number of alternative options available to patients with T3 tumors who wish to avoid upfront enucleation. One of these is dose escalation, which aims to achieve better tumor control, coupled with intravitreal bevacizumab to address the problem of increased toxicity (from higher doses) to normal ocular structures. A second option is the combination of hyperthermia and proton therapy. Hyperthermia is a known radiation sensitizer, and thus, a means of improving local control. The third alternative strategy is to address marginal failures better through more accurate modeling of the tumor [23]. High-risk patients could be candidates for combined treatment, such as systemic therapy with targeted agents and enucleation [21].

There are 2 main strategies for treating UM patients with no systemic metastasis, including eye-conserving therapies and enucleation [2]. Of these, RT techniques (which have a better than 90% success rate), including PBT, gamma-knife (GK) radiosurgery, plaque brachytherapy (PB), and transpupillary thermotherapy (TTT), as well as photodynamic therapy (PDT) are the most promising eye-preserving treatments for UM. However, they are not free of complications, including papillopathy and radiation maculopathy [14, 15, 29, 30].

Tumor size and intraocular location are thought to be the primary determinants of treatment modality choice [4, 6, 20, 21]. Although enucleation is unavoidable in some patients, given the large tumor size at the initial diagnosis, eye-preserving approaches are equally successful in terms of both survival and metastasis-free survival [6]. There is also an ever-increasing trend for early treatment (instead of more conservative monitoring) of small melanomas [2]. In the case of juxtapupillary CMs, there is no clearly and universally accepted management strategy. Several management strategies have been proposed, including enucleation, endoresection, charged particle RT, notched PR, and external beam stereotactic radiotherapy (SRT) or stereotactic radiosurgery (SRS) [9, 31]. In juxtapupillary CMs, the management focuses first on local tumor control and on the prevention of metastases and death [7, 32] and, secondarily, on eye retention, both for functional and cosmetic reasons [7]. When comparing the present state-of-the-art treatments, radiation (SRT, charged particle RT and PB) versus GK radiosurgery and laser TTT provide superior local tumor control, with mean failure rates of 19%, 21%, and 6%, respectively [10, 42].

In addition to surgery, laser therapy, and chemotherapy, RT is considered one of the most successful methods for the treatment of OM. Similar to all radiation treatments, in the case of OM, cancer cells are destroyed mainly by high-energy X-rays. External-beam RT is the most frequently used type of RT. This is in contrast to radiation treatments that are delivered using implants, that is, internal radiation therapy, also called brachytherapy, or plaque therapy. Finally, proton therapy is an external-beam radiation therapy that destroys cancer cells by using high-energy protons [4-6, 20].

The Collaborative Ocular Melanoma Study (COMS) was initiated with the express purpose of (a) determining whether patients with medium-sized CM showed prolonged survival with enucleation or brachytherapy, and (b) assessing whether preoperative radiation in patients with large CM have prolonged survival after enucleation [14, 17, 22]. The COMS results showed that patients with medium-sized CM did not have significantly different mortality rates at 12 years, irrespective of whether they were treated with PB or were subjected to enucleation. The apparent equivalence of treatments resulted in the exploration of episcleral PB, proton-beam treatment, and SRT as eye-preserving treatments [2, 7, 11, 14, 15, 21-23, 29, 31, 34, 35]. Following COMS, medium-sized or smaller CMs are treated mainly with brachytherapy [14, 22] while tumor control has been associated with a minimum dose to the tumor (D_{min}) of 85 Gy delivered to the apex of the tumor as the gold standard [14].

In the small melanoma arm of the COMS, the estimated mortality related to melanoma was 1% at 5 years and approximately 3.7% at 8 years [2]. However, the COMS excluded large melanomas. In the case of large melanomas, enucleation, either alone or following external beam therapy, was applied, but no difference in survival at 10 years was observed between the 2 treatments [2, 11]. Multivariable analysis of the COMS data identified that tumor height was a significant predictor of local failure, along with the location of the tumor, as juxtapupillary tumors presented a higher probability of local failure [14].

As in every case of collaborative studies, the accuracy of diagnosis of the condition is of cardinal importance. In this respect, the results of the COMS had a significant impact, given that the COMS reported a misdiagnosis rate of only 0.4 % [17, 36]. Of course, as in all similar studies, the COMS had its own limitations. Patients with peripapillary tumors appear to have a high rate of recurrence and metastases; thus, the COMS excluded these patients [23]. Apart from its limitations, however, the COMS has clearly influenced the evolution of RT during the last 20 years.

Radiotherapy Modalities

RT encompasses 3 treatment approaches: stereotactic fractionated radiotherapy (SFRT), PB, and charged particle RT (CPRT), which uses protons or helium-ions [4, 7, 10, 13-15, 17, 27, 28, 37]. Variations of these 3 treatment modalities are SRT and CPRT (which, in the case of OM, mainly refers to PBT), linear accelerator (LINAC)-based SFRT, and GK radiosurgery [13-15, 17]. Today, RT has become the treatment of choice for medium-sized and symptomatic small CMs [35].

RT uses X-rays, whereby high kinetic energy electrons (millions of electron volts or MVs) in the form of X-ray beams are directed at deep-seated tumors. The problem associated with this is the scattering of X-ray beams. Even when using synchrotron-based beams, which are focused and have scatter directed in the forward direction, RT lacks precision and therefore puts non-targeted organs near the tumor at risk of being damaged [38].

A focused kilovolt (kV) beam X-ray technique causes significantly less damage to critical structures of the eye than PB, costs less, and does not involve surgery. However, its principal disadvantage is that it delivers smaller doses to deep structures than MV beams. The solution to this problem of low dose is to use nanoparticles (NPs) with a high atomic number (Z). These NPs enhance the effect of kV X-rays to a point that is substantially more effective than MV beams, thereby achieving the desired therapeutic dose-concentration within the tumor [38].

Thus, NPs, which are non-toxic and are eliminated by renal clearance, are used to target the tumor precisely. To do this end, the method takes advantage of the enhanced permeability and retention effect and uses NPs that are attached to antibodies directed at tumor-specific antigens. Because the photoelectrons and the NP-emitted Auger cascade electrons appear in short ranges, they are more effective than radiation alone, because they damage only cells within the tumor boundaries. Thus, radiosensitization by NPs, whether in the kV or MV ranges, is much greater than other physical dose-enhancement methods. In the case of melanoma, the kV X-ray technique combined with eye immobilization and localization techniques results in ≤ 1.0 mm uncertainty, which is of particular importance in the treatment of CMs [38].

External Beam Therapy

Charged particle therapy along with GK and LINAC-based SRS are termed "external beam therapy techniques" [2, 39].

Charged Particle Treatment

Charged particles, such as protons, are used for therapeutic irradiation in charged particle treatment (CPT). Treatment is delivered either by using a LINAC for photon therapy (i.e., high-energy light), or by protons and other cyclotron-generated charged particles. Charged particles and photon irradiation differ in that the first provokes a smaller exit dose through normal tissue as they stop abruptly in the tissue (Bragg peak; a peak on the plot of the energy loss of ionizing radiation beam versus the distance it travels through matter). CPT has yielded promising results in the treatment of juxtapupillary tumors [14, 35]. Indeed, this group of treatment modalities showed low local failure rates. Thus, CPT yielded a local failure rate of 4.21%, while SRT yielded a failure rate of 6.20%, and PB had a failure rate of 9.45% [10].

Proton Beam Therapy

Although PBT is associated with more anterior segment complications, recent evidence shows that it has good eye retention rates [11]. The planning of PBT treatment for CM must always consider the lens, anterior chamber, and ciliary body volumes [22]. PBT can achieve local control rates of over 90%, which are sustained for 10 years [5, 20, 23]. Local control is improved by endoresection of the remaining part of the tumor [20] with a 5-year overall consistency within the 70%–85% range that is apparently, improving [5]. Large uveal tumors pose a particular challenge, because they are sometimes associated with increased local failure risk when treated conservatively [7, 11]. Death rates due to metastasis have not decreased despite the better local control achieved by the conservative treatment, which aimed to simultaneously control the tumor in the affected eye and maintain eye function completely as possible. [7]. Irradiating large volumes with exceedingly high doses increases complication rates, resulting in secondary enucleation [7, 11]. The increased risk of liver metastasis in these individuals is another concern, although there are reports based on murine models that PBT probably reduces metastasis rates [11]. It seems that enucleation is used more frequently in cases with ciliary body tumors, tumors with an anterior location, and tumors close to the optic disc or fovea. In addition, other factors that may increase the use of enucleation are the diameter and height of the tumor, dose of radiation, irradiation of the anterior segment, EOE, and ocular extension [7]. In histopathological terms, PBT causes necrosis, fibrosis, and balloon cells in the tumor tissue (i.e., PBT causes tumor degeneration), fewer mitoses, and damage to the tumor blood supply. However, although most tumors shrink, they do not disappear following irradiation [18]. Weber et al. found that the ocular recurrence-free rate is approximately 85% at 5-years for PBT in non-peripapillary UM, which was lower than the 90%–97% rate for medium-sized tumors. This is coupled with a metastasis-free survival rate of approximately 72% at 5 years, whereas the overall survival rate is almost 77%. Authors concluded that both of these are lower than the 80%-90%, mostly reported in the literature [21].

In a study that validated the AJCC staging system, which registered 3,800 individuals with melanoma, an 85% metastasis-free survival rate at 5-years was reported for stage 2 (stage IIa + IIb) patients. In another study of non-peripapillary CM and melanoma of the ciliary body that was treated with PBT, all ocular recurrences were located anterior to the equator, without recurrences occurring in the 36 patients who presented with tumors that were located posteriorly [21]. In cases where the tumor was located in the posterior pole (near the macula and the optic disc), vision function deteriorated by 33%–47% within 12–24 months after proton radiotherapy, while similar deterioration was reported in only 17%–28% of cases with tumors in other locations [20]. The doses utilized in older studies ranged from 56 to 60 Gy relative biological effectiveness (RBE), in 4 fractions, and up to 70 GyRBE, in 5 fractions [33]. However, no differences in local control and overall survival were noted at 5 years for a dose of 70 GyRBE (standard total dose) compared with those of a lower dose of 50 GyRBE, when both

treatments were delivered in 5 fractions over a span of 7-10 days. Similar rates of maculopathy and papillopathy have been observed between the 2 groups [14, 33]. However, at 5 years, a smaller visual field loss was recorded in the group treated with a reduced dose [33].

Hypofractionated PBT treatments contribute to the cost-effectiveness of PBT compared with tumors that require conventional fractionation [5]. The non-inferiority of PBT for metastasis and tumor survival has been amply demonstrated [28]. A local control rate of up to 98.9% at 5 years has been recorded in large groups of PBT-treated patients with iris, ciliary body, or CM, with a local recurrence rate of 6.1% at 5 years [40]. The reported 3% retreatment rate was attributable to recurrent tumor growth [28]. The ocular retention rate at 10 years is reported to range from 86.2% to 95% [40].

Following PBT, the tumor size shrinks, while sonographic internal reflectivity becomes significantly enhanced. However, tumor regression occurs anywhere from 6 months to 2 years [36]. Most local recurrences were reported in the first 3 years after treatment, while there is a reported case of an eye that developed a second CM after 20 years [19] following PBT for UM.

Complications of PBT include retinopathies, cataracts, glaucoma, optic neuropathy, and vitreous bleeding [5]. Neovascular glaucoma (NVG) is a major complication and a frequent cause of enucleation [7, 22, 28]. The greatest risk for enucleation is attributable to complications of PBT, mainly NVG, rather than to tumor recurrence [33]. NVG correlates with the volume of treatment and the dose delivered to the anterior segment that is contained in the treated field (particularly the ciliary body and lens) [33, 41]. Scar endoresection and aqueous shunt placement [5] have been used after PBT to control post-PBT glaucoma. However, therapies such as laser, intravitreal injections, and surgical endoresection have rendered PBT complications manageable [11, 28]. Microvasculopathy, including capillary occlusion and/or incompetence, are the main characteristics of radiation retinopathy following PBT. The initial damage to endothelial cells of the retinal capillary causes loss of these cells and vessel occlusion, first in retinal capillaries, followed by that of larger vessels (Table 2) [30].

Stereotactic Radiotherapy

SRT is used in the management of juxtapapillary CM because the delivery of an adequate dose is independent of tumor location on the optic disc [35, 39]. A suction fixation method has been described that involves retrobulbar anesthesia, followed by fixation of the eye by a circular vacuum chamber attached to the stereotactic head frame. Before GK radiosurgery, retrobulbar anesthesia is also used. Recent developments in non-invasive immobilization systems include the use of a thermoplastic mold for the immobilization of both the head and eyes while patients are "gazing forward," or by having the patients look at a fixation point using the melanoma-affected eye, while being monitored by video, or having the patient look at a fixed point of light [35].

Although PBT seems to be superior in maintaining healthy tissue, Hypofractionated SRT has the advantage in certain cases, particularly because no preoperative surgical marking is necessary, and because it is more cost-effective [2]. SRT utilizes a relocatable immobilization frame and can deliver irradiation in multiple fractions. On the other hand, GK irradiation employs a fixed immobilization frame anchored to the skull to ensure akinesia during single-dose radiosurgery [6, 31]. In cases of UM, LINAC-based SRT may be an alternative therapeutic option [6]. The advantages of SRT are summarized in Table 2.

There have been relatively few evaluations of the efficacy and complications of SRT in the treatment of UM with a sufficient follow-up time [31]. Radiation retinopathy (i.e., the appearance of clinically or angiographically confirmed retinal ischemic vasculopathy > 2 mm beyond the tumor margin, which may or may not involve the macula, and which is characterized by retinal hemorrhage, edema, infarcts, exudates, or neovascularization), may be present in 71%–88% of patients at ≥ 5 years after SRT treatment [10].

Comparison of treatment modalities

Proton Beam Therapy versus Brachytherapy

Particle beam therapy, when compared to brachytherapy, provides outcomes at least as good as those of PB [5, 33]. In a prospective randomized study comparing helium particle beam therapy with brachytherapy in patients who received particle beam therapy showed better local control (100% versus 84% after 5 years and 98% versus 79% after 12 years). The need for enucleation was higher after PB than after particle therapy (37% versus 17% at 12 years). The analysis also identified that the management modality used may be the most significant factor for the prediction of eye preservation, local control, and disease-free survival [33, 43].

Photon Beam Therapy versus Plaque Brachytherapy

PB provides local control equivalent to that of PBT (over 90%) [5]. Local control of posterior tumors by PBT was superior to that achieved with PB. This is attributed to the imprecise position of the plaque (particularly at the posterior pole) and suboptimal immobilization of the plaque. For anterior tumors, these 2 treatments are apparently equivalent [5, 11]. Although better results for local control were obtained with PBT than with brachytherapy, survival rates were comparable [7, 20]. PBT is more expensive and time-consuming than brachytherapy, and although PBT reduces the potential need for enucleation (due to complications) by 47% compared with brachytherapy [20], PBT can be accompanied by important side effects affecting the ocular and extra-ocular structures [7]. Because of the greater vision impairment associated with PBT than with brachytherapy [20], plaque therapy using ruthenium-106, cobalt-60, and iodine-125 is the preferred eye-preserving treatment for CM, as it is associated with slightly higher local control rates than PBT [22].

Proton Beam Therapy versus Stereotactic Radiotherapy

SRT and PBT have comparable local control outcomes when used in CMs [23]. Surgical insertion of localization clips in patients with melanomas seems to be an advantage of SRT. However, delineating the extent (borders) of the tumor based only on CT images, which is the method used in SRT, is challenging. Therefore, other techniques may complement CT, including digital fundus photography, MRI, or radiographic techniques using intravenous contrast agents. In addition, carbon-ion RT and PBT present comparable local control rates in cases of CM [22]. Furthermore, large studies have confirmed that both PBT and SRT provide local control in the order of 95%–97%. It should be noted that PDT differs from PBT and SRT in that it stabilizes or even improves the patient's vision, while patients undergoing PBT or SRT can expect a visual loss of ≥ 3 lines on a Snellen chart in 45%–65% of cases [17].

Plaque Brachytherapy versus Stereotactic Radiotherapy

No serious comparisons (e.g., randomized control trials) have been reported between SRT and PB in the treatment of CM. Moreover, no statistically significant differences have been reported between SRT and PB in terms of local control [10].

Transpupillary Thermotherapy versus Plaque Radiotherapy

Compared with PR, TTT results in rapid tumor regression, and brachytherapy is associated with more severe and diffuse side effects and complications than TTT [32].

Photodynamic Therapy versus Transpupillary Thermotherapy and Photocoagulation

Efforts to introduce photocoagulation and TTT for small CMs have been abandoned because of the reported high recurrence rate. However, PDT applied in pigmented and non-pigmented CMs achieves good tumor control rates [16].

Hence, the outcomes of different irradiation regimens depend on several factors, including tumor size, plaque size, radiation dose, and the amount of tissue that is damaged by radiation [27]. Decisions regarding small tumors should be based on the presence of indications for malignant transformation and the inherent risks of treatment [2]. The AJCC classification is a valuable prognostic tool. Although in *c*T2 and in most *c*T1 classifications (i.e., 3.1–6.0-mm tumor thickness), local RT, PR, or PBT are used [16], there is no universal agreement on the optimal management option for patients with T3 tumors [23]. Many cases with *c*T3-4 tumors are treated by primary enucleation with conservative treatments, yielding variable results [16].

Therefore, UM treatment can follow 1 of 2 strategies: eye-conserving therapies or enucleation [2]. Despite their complications (i.e., papillopathy and radiation maculopathy) [14, 15, 29, 30], RT techniques (with > 90% success rate) seem to be more promising, including PBT, GK radiosurgery, and PB, along with TTT and PDT. Moreover, RT may be among the most successful methods used for the treatment of OM [4-6, 20].

The COMS results indicated that, irrespective of whether PB or enucleation was used, medium-sized CMs did not have significantly different mortality rates at 12 years. Thus, new eye-preserving treatments, including episcleral PB, PBT, and SRT, have been explored [2, 7, 11, 23, 29]. Following the COMS, medium-sized or smaller CMs have been managed mainly with brachytherapy [14, 22] which has become the treatment of choice in the case of medium-sized and symptomatic small CMs [35]. Following the COMS, medium-sized and smaller CMs are managed mainly with brachytherapy.

Compared to brachytherapy and SRT, proton therapy is applicable to a wider range of tumors and can be used in

the treatment of both posterior peripapillary tumors and anteriorly located tumors [4, 20, 21, 23, 33, 40]. Despite the fact that, theoretically, choroidal, ciliary body, and iris melanomas can be treated with PBT, the visual acuity prognosis and rates of eye conservation for large melanomas remain low [2]. PBT is particularly suited for cases where brachytherapy is not advised, including large tumors or cases with extrascleral extension [21]. The physical properties of PBT (i.e., beginning with a low dose, followed by an increased dose to the target as per the Bragg peak, and finally a rapid fall-off, distal to the target) makes PBT attractive for treating the eye [2, 4, 5, 20, 21, 28, 34, 40].

The present review focused on the most recent literature, published in the last decade, and deposited in 4 widely used databases: PubMed, MEDLINE, Google Scholar, and GeneCards. It also highlights the most recent RT modalities used in the management of UMs. In addition, it refers to appropriate management approaches for melanomas of different classes. However, many of the articles found in the literature utilized different methodologies and described small samples with specific patient characteristics. Thus, the results may not necessarily apply to all UM patients. Moreover, it is difficult to compare the results of the treatments used for melanomas with different characteristics effectively. Future studies should aim to investigate the use of the most efficient method or combination of methods for the individual and to determine the most appropriate timing for the selected treatment to achieve better results. Furthermore, it is crucial to compare different types of management in patients with small-, medium-, or large-sized melanomas, or melanomas at specific locations, more thoroughly. In addition, robust study designs, such as randomized clinical trials, may be able to provide more reliable and applicable results.

CONCLUSIONS

Overall, OM may be treated with different strategies, depending on the tumor characteristics, including size, thickness, and location. At present, there is no gold standard for the management of all OMs, but each case should be approached individually to minimize ocular manifestations and extraocular metastasis, if possible. Further research is needed to explore the results of different treatment modalities in patients with metastatic or non-metastatic OM with different characteristics.

ETHICS DECLARATIONS

Ethical approval: This is a review study and no ethical approval was needed.
Conflicting of interests: None.

FUNDING

None.

ACKNOWLEDGEMENTS

None.

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