Stereotactic radiotherapy for uveal melanoma: A case report

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Received November 7, 2023; Accepted January 9, 2024

DOI: 10.3892/mco.2024.2721

Abstract. Uveal melanoma (UM) is the most common primary intraocular malignancy worldwide. Surgical intervention and radiation therapy (RT) are the primary treatment options. Given the complexity and cosmetic discomfort associated with eye enucleation, this method is less frequently used. As a result, RT, including photon therapy, proton therapy and brachytherapy, has become the treatment of choice. Traditionally, plaque brachytherapy has been the most commonly used in clinical practice. However, the question of which type of radiation therapy is the most effective, safe, commonly available and cost-effective remains open. The present study provided a follow-up analysis of a patient with UM who was treated using the image-guided volumetric modulated arc therapy (IG-VMAT) technique. A complete response without complications and symptom relief were noted one and a half years after treatment. The present findings suggest that photon external beam radiotherapy using the IG-VMAT technique may offer a viable and safe alternative for the management of UM. This approach potentially sidesteps the complex and morbid aspects of surgical intervention and plaque brachytherapy. Owing to the limited sample size, a more robust understanding of the efficacy and safety of this treatment will require the analysis of additional cases. Further research with a larger cohort is essential to validate these preliminary observations.

Introduction

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults (1,2), but it is still considered a rare cancer with ~5-6 new cases per million individuals per year worldwide (3,4). According to the Collaborative Ocular Melanoma Study (COMS), the precision of UM diagnosis has increased markedly from ~20 to >99% in recent years (5). Originating in the uveal tract of the eye, which comprises the iris, ciliary body and choroid, this neoplasm poses not only a significant risk to vision, but also a considerable metastatic potential. The 5-year overall survival rate for metastatic UM is 80.9% (6,7). Despite advancements in diagnostic methods and treatment modalities, survival rates have not significantly improved over the past few decades.

The most common treatment options are surgical interventions (such as local tumor resection and enucleation of the eye) and radiation therapy (RT), including proton beam radiotherapy (PBRT), photon (RT) radiotherapy (RT), stereotactic body radiation therapy (SBRT), stereotactic radiosurgery and brachytherapy. These treatments are often associated with varying degrees of success and complications. Local recurrence is linked to shorter life expectancy, highlighting the importance of the initial choice of treatment (8). The treatment choice depends on the extent of the primary process, the availability and experience of treatment methods and patient preferences.

Although plaque brachytherapy using ophthalmic applicators and eye enucleation are the most available treatment options for UM worldwide (9), PBRT and SBRT are being increasingly employed. These methods have been proven to be both effective and safe. Radiotherapy is the most common eye globe-conserving therapy for UM. The COMS demonstrated that radiation therapy with iodine-125 (^{125}I) is as effective as enucleation in preventing metastases (10). With SBRT, the 5-year local tumor control (LC) rate was 92.2% and progression-free survival (PFS) was 77.0% (11). With CyberKnife radiosurgical systems, the 5-year LC and PFS rate was 73.0 and 57.0%, respectively (12). PBRT was determined to have a 5-year LC rate of 90% (13).

Numerous studies have shown that photon irradiation delivers an adequate dose to the target area, similar to PBRT (14,15), while achieving satisfactory treatment results (16-18). Long-term follow-up results for SBRT are more limited than those for other radiotherapy modalities, although available studies indicate similar rates of local control and distant metastatic disease (19-21).

Case report

A 79-year-old female patient was regularly followed up for macular degeneration and cataract of the left eye at an external

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Key words: uveal melanoma, stereotactic body radiation therapy, radiotherapy

hospital. The patient had been diagnosed with a choroidal nevus in 2016. The patient's medical history included a pigmented nevus located nasally from the optic disc in the left eye and right breast cancer (in 2015), which had been in remission for six years. During ophthalmoscopy in 2016, a protruding lesion with sharp edges measuring 7x9 mm and hyperpigmentation was discovered nasally from the optic disc in the left eye (Fig. 1).

In October 2021, the patient came to our hospital (European Medical Center, Moscow, Russia), and magnetic resonance imaging (MRI) of the orbits revealed a tumor in the posterior part of the left eyeball, adjacent to a wide base to the membranes of the eye, measuring 12x7x9 mm, accumulating a contrast agent with limited MR diffusion indicators (Fig. 2A and B).

Taking into account the history of right breast cancer, whole-body positron emission tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (^{18}FDG) was performed to exclude distant metastatic lesions. A neoplasm was detected on the posteromedial surface of the left eyeball with low accumulation of radiopharmaceuticals (maximum standardized uptake volume, 2.52), as shown in Fig. 2C.

Thus, based on ophthalmoscopy, MRI data, ultrasound, ^{18}FDG PET/CT and the presence of a pigmented nevus in the anamnesis, a diagnosis of choroidal melanoma cT2aN0M0 without histological verification was established.

All treatment options and possible side effects were discussed. The patient refused surgery and agreed to undergo RT. Considering the diameter and thickness of the tumor, the patient's refusal to undergo surgery and the unavailability of proton therapy, an interdisciplinary meeting consisting of a medical oncologist, radiation oncologist and ophthalmologist the decision was held and it was decided to perform SBRT on the linear accelerator Varian EDGE Radiosurgery system (Varian Medical System) using the image-guided volumetric modulated arc therapy (IG-VMAT) method. The delineation of the tumor in the three projections and the dose distribution are shown in Fig. 3.

In January 2022, radiation therapy of the posterior choroid of the left eye was administered with a single dose of 10.0 Gray (Gy) x5 fractions, adding up to a total dose of 50.0 Gy. The dose-volume histograms and dose distribution in the organs at risk (OARs) plan evaluations are shown in Fig. 4 and Table I. The patient's head was then fixed using a thermoplastic mask. By performing several CT simulations with different views of the patient, the internal target volume was formed, taking into account the possible amplitude of tumor movement during treatment.

The main radiobiological effects of radiosurgery are damage to the vascular endothelium and the subsequent apoptosis of endothelial cells (22). This radiobiological effect simultaneously reduces the activity of the subretinal neovascular membrane. The next administration of an anti-VEGF treatment (brolucizumab), which the patient had previously taken regularly for the treatment of retinal dystrophy, was required 10 months after irradiation. Ophthalmological examination showed an improvement in visual acuity from 0.3 in October 2021 to 0.8 in September 2022.

On control MRIs, a gradual decrease in tumor size was observed, as shown in Fig. 5A. A complete response was achieved 1 year after treatment (Fig. 5B).

Table I. Dose distribution in the organs at risk, GTV and PTV.

Item	Volume, cm^3	Maximum dose (<0.035 cm^3), Gy	Mean dose, Gy
PTV	1.0	52.3	51.3
GTV	0.6	52.3	51.4
Lt. optic nerve	0.5	22.3	7.8
Lt. lens	0.2	23.1	8.7
Lt. eye	7.5	52.3	20.4
Rt. optic nerve	0.4	0.2	0.1
Rt. eye	6.3	0.1	0.1
Chiasm	0.5	4.7	0.5

PTV, planning target volume; Lt, left; Rt, right; GTV, gross tumor target volume.

No early or late radiation complications were noted over the period of 1.5 years. No evidence of disease progression or relapse was observed according to control MRI data from June 2023. Currently, the patient is being actively monitored.

Discussion

The genetic profile of UM distinguishes it from other tumor types, making the selection of systemic therapy difficult. Although UM tumors exhibit a relatively low mutational burden, they are characterized by certain recurrent mutations. Typically, UM tumors possess an initiating mutation in either guanine nucleotide-binding protein G(q) (GNAQ) or G protein subunit alpha 11 (GNA11), followed by secondary mutations in genes such as eukaryotic translation initiation factor 1A X-linked, splicing factor 3b subunit 1, serine and arginine rich splicing factor 2 or BRCA1 associated protein 1, which are the focus of most research (23-25). In particular, mutations in GNAQ and GNA11, present in >80% of UM cases, have been the focus of targeted therapy research, with inhibitors such as protein kinase C (PKC), mitogen-activated protein kinase kinase inhibitors, and mesenchymal-epithelial transition factor (MET) inhibitors. Most studies have shown either limited effectiveness or ineffectiveness of therapies targeting these inhibitors (26-28). Crizotinib, an inhibitor of MET that is highly expressed in the UM, has shown encouraging results in preclinical models. However, its use as an adjuvant in patients with high-risk UM did not reduce the relapse rates in a phase II trial and had numerous side effects (29). Park *et al* (30) concluded in their study that UM cells have complex, PKC-independent signaling pathways that contribute to their survival and resistance to targeted therapies. In addition, the preferentially expressed antigen in melanoma and epigenetic modifications have emerged as novel biomarkers that can potentially guide personalized treatment strategies (31). However, the heterogeneity within UM subpopulations necessitates further investigation to determine the efficacy of therapies that target these molecular aberrations. Of note, there is no specific systemic therapy regimen for UM and most studies have focused on metastatic disease.

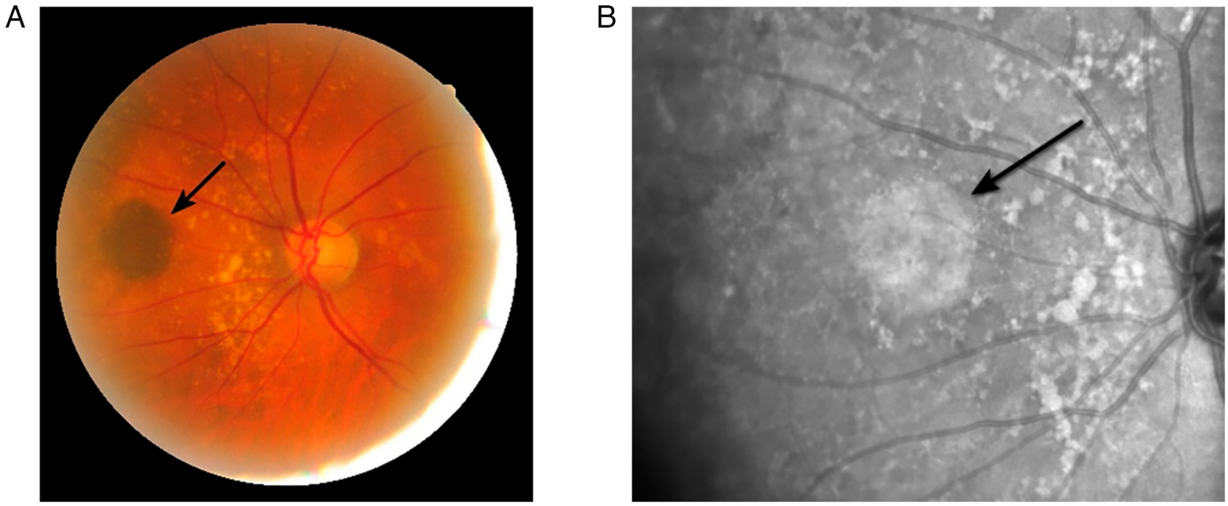

Figure 1. (A) Ophthalmoscopy (May 2016). The black arrows indicate a hyperpigmentation lesion with sharp edges measuring 7x9 mm nasally from the optic disc in the left eye. (B) Ocular fundus in the infrared spectrum.

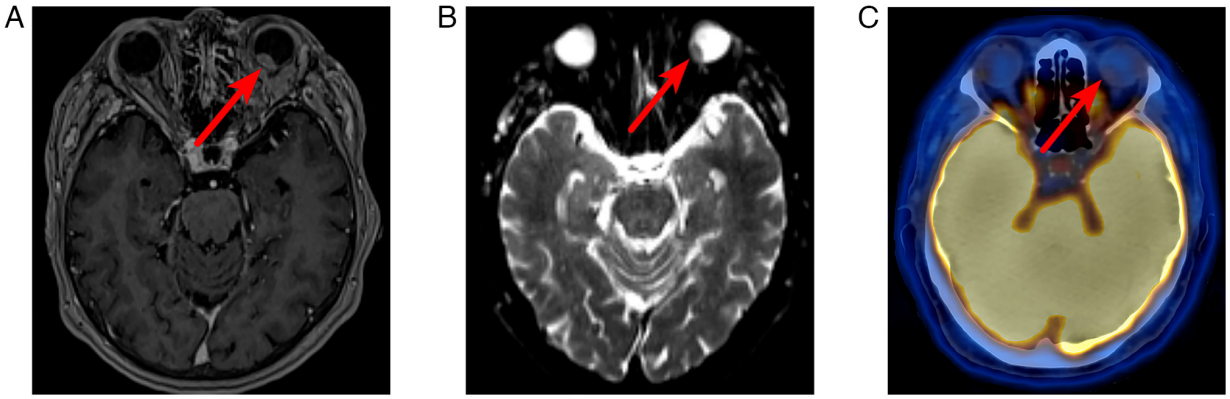

Figure 2. Orbit MRI with i/v contrast from October 2021. (A) T1-weighted image and (B) T2-weighted image. The red arrows indicate homogeneous contrast uptake in the posterior part of the left eyeball, adjacent with a wide base to the membranes of the eye, measuring 12x7x9 mm. (C) Initial ^{18}F-fluorodeoxyglucose positron emission tomography/CT. The red arrow indicates a low accumulation of radiopharmaceuticals (maximum standardized uptake volume, 2.52).

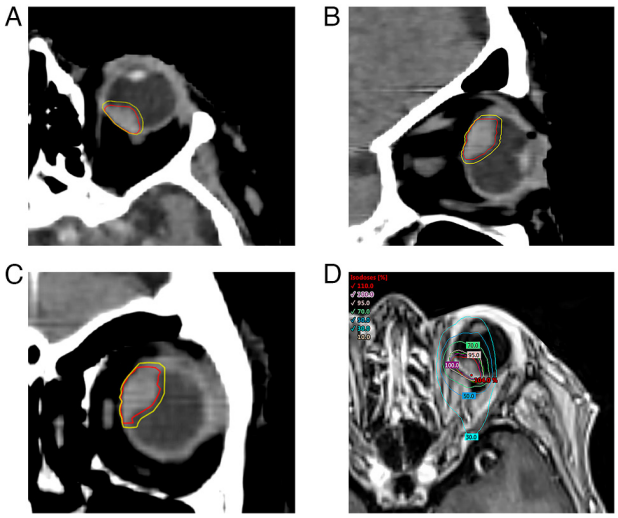

Figure 3. Mapping of the treated lesion of the patient, based on the pre-irradiation therapy brain CT scan fused with the brain MRI in three projections: (A) Axial plane, (B) sagittal plane, (C) frontal plane during the treatment planning. (D) Dose distribution for stereotactic body radiation therapy using the image-guided volumetric modulated arc therapy method. The color wash represents the dose in Gy.

According to the National Comprehensive Cancer Network Guidelines v.1.2023, which divide UM according to tumor size, the patient of the present study belongs to the second category (32). The main treatment methods for the second category of the disease are brachytherapy and radiation therapy with protons or photons. The COMS randomized trial noted no significant difference in survival rates in patients with medium-sized UM after enucleation compared with ^{125}I brachytherapy after a 15-year follow-up period (10). PBRT is associated with a minimal risk of local tumor recurrence in cases of UM. A significant number of PBRT studies have demonstrated high LC rates after treatment (33-35). Despite the success of PBRT in the treatment of UM, there is a problem with the availability of proton therapy for patients worldwide. At the beginning of 2023, according to the Particle Therapy Co-Operative Group data (36), 89 proton centers were used for the treatment of diseases worldwide, including facilities in scientific research institutes. Most of these are located in the USA-49, Japan-19 and Germany-5. In this context, the advantage of SBRT is its wide accessibility, based on linear accelerators commonly used in the majority of RT departments.

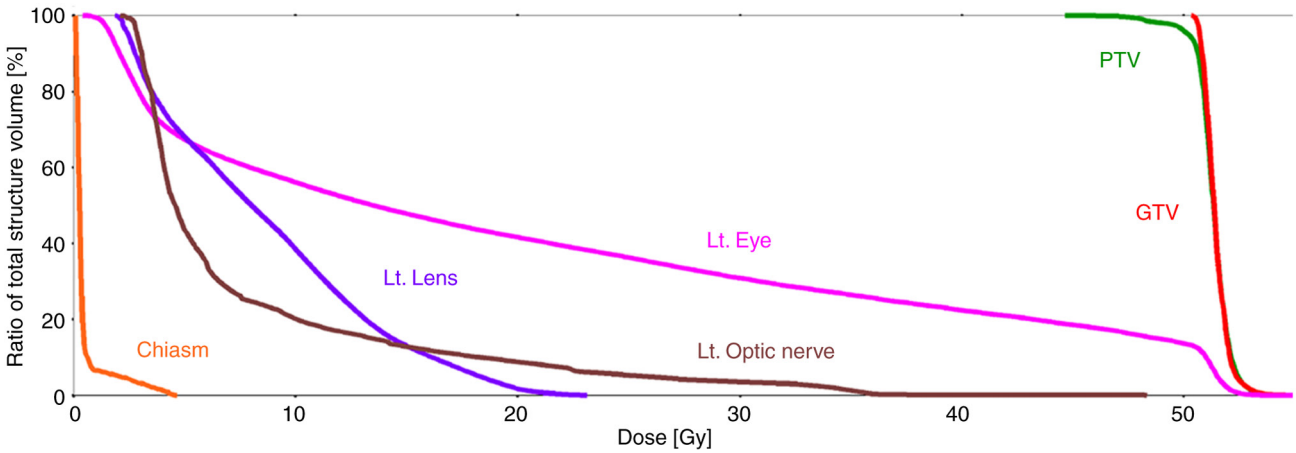

Figure 4. Dose volume histogram. PTV, planning target volume; Lt, left; GTV, gross tumor target volume.

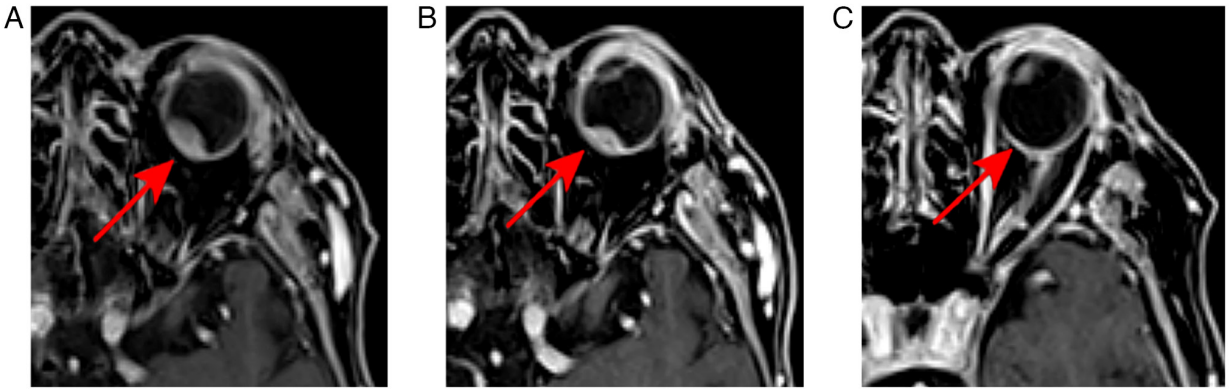

Figure 5. (A) Initial orbit MRI with i/v contrast. The red arrow indicates the tumor before treatment. (B) Orbit MRI with i/v contrast. The red arrow indicates the decrease in tumor size in the left eye six months after radiation therapy. (C) Final orbit MRI with i/v contrast a year after radiation therapy. The red arrow indicates complete response in the left eye.

Weber *et al* (14) conducted a comparative study of PBRT and SBRT using the intensity-modulated radiation therapy (IMRT) technique in the treatment of UM. The results showed that PBRT and SBRT had similar dose distributions in the treatment of UM. However, to achieve the treatment planning goal and dose constraints of OARs organs at risk, the SBRT method requires a large number of non-coplanar beams. Furthermore, the modern radiotherapy-IMRT method did not improve the dose distribution compared with single-field non-IMRT (14). VMAT is an improved version of IMRT, which represents a sophisticated iteration of IMRT that involves rotating one or more beams of radiation around the patient (37).

IG-VMAT delivers a high-power, targeted dose of radiation with minimal damage to the surrounding tissue (38). SBRT using VMAT has proven to be an effective and safe method for treating both solid tumors and metastases, regardless of their location in the body (39).

In SBRT, multiple photon beams converge on the tumor from different directions, delivering a concentrated radiation dose to the tumor and minimizing collateral damage to surrounding healthy tissue. Jager *et al* (40) also consider photon radiation therapy as the most acceptable treatment option for UM, taking into account both the effectiveness and availability of the method. In a study by Akbaba *et al* (41), the authors concluded that SBRT is an effective treatment method for UM with a high level of local control and a 2-year vision retention rate comparable to brachytherapy or PBRT, even available in numerous radiation oncology departments and easy to implement.

It is also worth noting that several adverse reactions may occur during radiation therapy. The development of cataracts is a common eye complication resulting from radiotherapy, with risk factors including an overall dose exceeding 12 Gy and the presence of anterior tumors; there is a 65-90% risk of cataract development. After radiotherapy, maculopathy and optic nerve neuropathy manifest in ~25 and 8-14% of patients, respectively, and significantly impair visual acuity (42). It is crucial to recognize that adverse events are associated with any treatment approach used for UM (43,44). Tumor location, size, volume and total radiation dose were the primary risk factors for these adverse events. In the present case, we did no adverse events related to early or late RT were observed.

In conclusion, the management of UM continues to evolve, with an array of therapeutic modalities. Used for primacy. SBRT using IG-VMAT has emerged as a potent, reliable and efficacious method for treating UM, which was used in the patient of the present study. Its flexibility, precision and capacity to deliver high doses of targeted radiation while sparing surrounding healthy tissues accentuate its prominence.

In addition, SBRT's broad accessibility due to the prevalence of linear accelerators in most RT departments ensures that a larger patient demographic can benefit from this state-of-the-art treatment. The results from our case, coupled with the growing body of supportive literature, suggest that SBRT may be an alternative to PBRT. As healthcare professionals continue to prioritize both treatment efficacy and patient quality of life, SBRT stands out as a viable, eye-conserving and commonly available treatment for UM. Future research with a larger cohort is essential to validate these preliminary observations.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

All authors (NS, IL, AS, OL, IP and KT) contributed to the study conception and design. Material preparation, data collection and analysis were performed by NS, IL, AS and KT. The first draft of the manuscript was written by IL and AS, and all authors commented on previous versions of the manuscript. Images were prepared by IL. NS and IL confirm the authenticity of all the raw data. The final version of the manuscript was completed by KT. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval for the study was obtained from the Local Research Ethics Committee (European Medical Center, Moscow, Russia) dated April 16, 2019.

Patient consent for publication

Written consent for publication of this case report including all images was obtained from the patient.

Competing interests

The authors have no competing interests to disclose.

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