https://doi.org/10.5114/oku/199411 (Reviews Papier)

Received: 12.06.2024 Accepted: 24.07.2024

# Principles of Management of Patients after Uveal Melanoma Radiotherapy in Ophthalmic Practice

**Joanna Kowal[1,2], Magdalena Dębicka-Kumela[1,2], Agnieszka Nowak[1], Karolina Gerba-Górecka[1], Dagmara Nowak[1], Bożena Romanowska-Dixon[1,2]**

[1] Department of Ophthalmology and Ocular Oncology, University Hospital in Krakow, Poland
Head: Prof. Bożena Romanowska-Dixon, PhD (hab.), MD
[2] Department of Ophthalmology, Jagiellonian University Medical College, Krakow, Poland
Head: Prof. Bożena Romanowska-Dixon, PhD (hab.), MD

**Summary:** The most commonly used treatment for uveal melanoma is radiotherapy. In the months directly following irradiation, patient management should focus on controlling uveitis and monitoring intraocular pressure, alleviating pain, and preventing postoperative infections. If exudative retinal detachment occurs, surgical intervention is not recommended. The detached retina typically reattaches spontaneously as the tumor regresses and vascular leakage diminishes. In cases of choroidal detachment, patient observation is sufficient. For late post-radiation complications, such as retinopathy, neuropathy, and post-radiation maculopathy, treatment with anti-VEGF injections into the vitreous chamber is indicated. Initial therapy consists of three injections at two-month intervals, with continued anti-VEGF treatment as necessary, based on the patient's response. Cataract surgery is also recommended, when clinically indicated.

**Key words:** uveal melanoma, radiotherapy, management after brachytherapy, radiation-induced complications.

## Introduction

Uveal melanoma (UM) is a malignant tumor with an annual incidence of 6–7 cases per million population per year. Its incidence increases with age, rising from approximately 2.5 per million/ per year in individuals aged 15–44 to 25 per million/ per year in those over the age of 65. UM is more prevalent among Caucasians. It is estimated that 200–300 new cases of UM are diagnosed annually in Poland [1–5].

The most commonly used treatments for uveal melanoma are radiotherapy methods, including brachytherapy (BT) and proton radiotherapy [1, 3, 6–8]. The goal of radiotherapy is to damage the DNA of cancer cells, thereby inhibiting tumor growth and preventing its spread to other bodily organs via the bloodstream. However, radiation can also harm the DNA of normal cells, leading to potential side effects. The primary objective of radiotherapy is to target the tumor while minimizing damage to surrounding healthy tissues [9–11]. Long-term studies show that brachytherapy and proton therapy offer survival rates comparable to those of ocular enucleation [12].

## Patient management

Patients treated for UM are rarely encountered in the routine practice of ophthalmologists in outpatient clinics. However, when such contact occurs, it may raise concerns about the appropriate post-surgical and/ or post-irradiation management of the tumor.

As a standard, the first follow-up visit at a local ophthalmology clinic is recommended within seven days of patient discharge from the hospital. The goal of this visit is to assess the healing of the ocular surface and to check for any signs of inflammatory reaction. At this early stage, it is not possible to evaluate the efficacy of the treatment. In fact, the melanoma may seem to enlarge initially due to edema, bleeding, and an inflammatory response in tumor tissue. This is not an indication of a negative outcome. The first post-treatment check-up at the facility where radiotherapy was performed is scheduled four to five months after the completion of treatment. The need for additional early follow-up examinations is determined by the physician at the patient's local outpatient clinic. Subsequent follow-up appointments are scheduled individually, based on the local condition.

As standard practice, the following topical treatments are recommended after the procedure:

1. a mydriatic (1% atropine, 1% tropicamide, or 0.5% tropicamide) for up to one month;
2. a steroid and/or non-steroidal anti-inflammatory drugs (NSAIDs) for up to one month;
3. an antibiotic ointment – up to 10 days.

During the first months after irradiation, attention should be given to symptomatic treatment, with the aim to:

1. suppress the inflammatory process in the uvea (prevent the formation of iris synechiae) through the use of long-acting mydriatics and corticosteroids;
2. control intraocular pressure, e.g. with antiglaucoma medications;
3. reduce pain, when necessary, e.g. with commonly used analgesics;
4. prevent postoperative wound infection;
5. prevent secondary non-rhegmatogenous retinal detachment through the use of long-acting mydriatics during the initial months of treatment, along with a sparing lifestyle and avoidance of physical exertion. The detached retina will spontaneously reattach as the tumor regresses and vascular leakage decreases, so surgical treatment is not recommended;
6. monitor to assess whether choroidal detachment has occurred; if so, patient observation and topical steroid administration are indicated.

Possible complications after radiotherapy can be classified into early and late [3, 13–15].

In the early postoperative period, the following may occur: redness; edema; petechiae in the conjunctiva, eyelids, and orbital tissues; inflammatory reaction; increase in retinal detachment

accompanying the tumor (which may worsen visual acuity and reduce the field of vision after the procedure); choroidal detachment (requiring only observation); vitreous hemorrhage; increased intraocular pressure; and transient diplopia. Treatment for these complications is symptomatic only [12].

Late complications following radiotherapy include:

1. radiation retinopathy, which can manifest as vessel occlusion, formation of retinal exudates and petechiae, and neovascularization. Treatment involves injections of anti-vascular endothelial growth factor (anti-VEGF) inhibitors into the vitreous chamber, with an initial treatment regimen of three injections at 1–2 month intervals. Subsequent drug doses depend on the local condition and are administered individually as needed [1, 16];
2. radiation maculopathy, which is the most common cause of visual acuity deterioration. Irradiation of tumors located within 6 mm of the fovea leads to maculopathy in 64% of patients. Treatment involves injections of anti-VEGF preparations into the vitreous chamber according to the protocol outlined above [1, 17, 18];
3. radiation neuropathy, characterized by edema of the optic disc (cranial nerve II), along with the presence of hard or soft exudates and petechiae. Neuropathy typically develops 31 months (range: 13–49 months) after the completion of radiotherapy. In such cases, anti-VEGF injections into the vitreous chamber are administered [1, 13];
4. secondary glaucoma, which arises due to radiation-induced changes in the retina and/or irradiation of the ciliary body and drainage angle area. The prevalence of this complication ranges from 3% to 56% [19, 20]. In treatment, topic anti-glaucoma medications are used, with dorzolamide administered systemically when necessary. There are no contraindications to antiglaucoma surgery that avoids the tumor base area. Secondary glaucoma is the most significant factor affecting the prognosis for preserving the eye after irradiation, occasionally resulting in ocular enucleation despite a favorable therapeutic response and effective local tumor control [13, 14];
5. complicated cataract;
6. dry eye syndrome, which is treated with preservative-free moisturizing eye preparations.

If the local treatment yields a favorable result, there are no contraindications to surgical procedures. However, during surgery, it is advisable to avoid the scar or any remaining tumor tissue.

The first follow-up ultrasound (USG) or ultrabiomicroscopy (UBM) examination to assess tumor size is recommended approximately four months after radiotherapy. Depending on the treatment outcome, subsequent follow-up visits at the treatment center may be scheduled every one to two years. The recommended frequency of follow-up appointments at the patients' local ophthalmology outpatient clinics is every six months [1].

It is crucial to remember that uveal melanoma can metastasize and, like all malignant tumors, requires ongoing comprehensive care. The organs most at risk for metastasis include the liver, lungs (less commonly), skin, subcutaneous tissue, and others [1–3, 21]. It is essential to remember about regular internal medicine or oncology assessments. Periodic examinations should be carried out at least twice a year, including magnetic resonance imaging (MRI), computed tomography (CT), or abdominal ultrasound (unless a greater frequency of assessment is advised) and liver function tests (AST, ALT). Additionally, a chest X-ray should be performed once a year [1, 3, 22]. A positron emission tomography (PET) scan may also be conducted.

## Conclusions

The management of patients reporting to their local ophthalmology outpatient clinic after radiotherapy for uveal melanoma should focus on symptomatic treatment for both early and late post-radiation complications, ordering general examinations, and referral to the treatment center for further evaluation if tumor recurrence (e.g., an increase in tumor size) is suspected.

**Disclosure**
Conflict of interests: none declared
Funding: no external funding
Ethics approval: Not applicable.

## References:

1. Romanowska-Dixon B, Jager MJ, Coupland SE: *Onkologia Okulistyczna*. PZWL Wydawnictwo Lekarskie. Warszawa 2019: 22, 249–272, 295–305, 314–318.
2. Collaborative Ocular Melanoma Study Group: *The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma. V: 12-year mortality rates a prognostic factors: COMS report No 28*. Archives of Ophthalmology. 2006; 124: 1684–1693.
3. Romanowska-Dixon B, Jakubowska B: *Czerniak błony naczyniowej. Diagnostyka różnicowa nowotworów wewnątrzgałkowych*. Wydawnictwo Uniwersytetu Jagiellońskiego. Kraków 1014: 23–30, 27–100.
4. Isager P, Ehlers N, Overgaard J: *Have choroidal and ciliary body melanomas changed during the period 1955-2000?* Acta Ophthalmol Scand. 2004; 82(5): 509–516.
5. Romanowska-Dixon B, Pogrzebielski A, Bogdali A i wsp.: *Radioterapia protonowa czerniaka błony naczyniowej - wstępne wyniki*. Klin Oczna. 2012; 114(3): 173–179.
6. Reichstein DA, Brock AL: *Radiation therapy for uveal melanoma: a review of treatment methods available in 2021*. Curr Opin Ophthalmol. 2021 May 1; 32(3): 183–190.
7. Foti PV Travali M, Farina R, et al.: *Diagnostic Methods and Therapeutic Options of Uveal Melanoma with Emphasis on MR Imaging - Part II: Treatment Indications and Complications*. Insights Imaging. 2021; 12: 67.
8. Jager MJ, Shields CL, Cebulla CM, et al.: *Uveal Melanoma*. Nat Rev Dis Primers. 2020; 6: 24.
9. Baskar R, Lee KA, Yeo R, et al.: *Cancer and Radiation Therapy: Current Advances and Future Directions*. Int J Med Sci. 2012; 9: 193–199.
10. Reichstein DA, Brock AL: *Radiation Therapy for Uveal Melanoma: A Review of Treatment Methods Available in 2021*. Curr Opin Ophthalmol. 2021; 32: 183–190.
11. Rusńak Ś, Hecova L, Kasl Z, et al.: *Therapy of Uveal Melanoma. A Review*. Czech Slovak Ophthalmol. 2021; 77: 3–15. doi: 10.31348/2020/10.
12. Diener-West M, Earle JD, Fine SL, et al.: *The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma. III: initial mortality findings. COMS Report No 18*. Archives of Ophthalmology. 2001; 119: 969–982.
13. Banou L, Tsani Z, Arvanitogiannis K, et al.: *Radiotherapy in Uveal Melanoma: A Review of Ocular Complications*. Curr Oncol. 2023 Jul; 30(7): 6374–6396.
14. Kowal J, Romanowska-Dixon B: *Ocena odległych powikłań po brachyterapii I-125 czerniaka błony naczyniowej*. Klin Oczna. 2016; 118 (3): 226–230.
15. Kamrava M, Lamb J, Soberón V, et al.: *Ocular Complications of Radiotherapy*. In Clinical Ophthalmic Oncology; Springer International Publishing: Cham, Switzerland, 2019; pp. 117–128.
16. Finger PT, Chin KJ, Semenova EA: *Intravitreality-VEGF therapy for macular radiation retinopathy: a 10 years study*. Europen Journal of Ophthalmology. 2016; 26: 60–66.
17. Kinyoun JL: *Long-term visual acuity results of treated and untreated radiation retinopathy (An AOS Thesis)*. Transactions of the American Ophthalmological Society. 2008; 106: 325–335.
18. Horgan N, Shields C, Mashayekhi A, et al.: *Classification and treatment of radiation maculopathy*. Current Opinion in Ophthalmology. 2010; 21: 233–238.
19. Mazzini C, Pieretti G, Vicini G, et al.: *Clinical Outcomes and Secondary Glaucoma after Gamma-Knife Radiosurgery and Ruthenium-106 Brachytherapy for Uveal Melanoma: A Single Institution Experience*. Melanoma Res. 2021; 31: 38–48.
20. Romanowska-Dixon B, Markiewicz A: *Jaskra następcza po brachyterapii u chorych z czerniakiem naczyniówki i ciała rzęskowego*. Okulistyka. 2008; XI: 60–64.

**21.** Kujala E, Makitie T, Kivela T: *Very long-term prognosis of patients with malignant uveal melanoma.* Investigative Ophthalmology & Visual Science. 2003; 44: 4651–4659.

**22.** Diener-West M, Reynolds SM, Agugliaro DJ, et al.: *Collaborative Ocular Melanoma Study Group. Report 23. Screening for metastasis from choroidal melanoma: The Collaborative Ocular Melanoma Study report 23.* Journal of Clinical Oncology. 2004; 22: 2438–2444.

**Adres do korespondencji/ Reprint requests to:**
Joanna Kowal (e-mail: joanna.1.kowal@uj.edu.pl)
Oddział Kliniczny Okulistyki i Onkologii Okulistycznej Szpitala Uniwersyteckiego w Krakowie
ul. Kopernika 38, 31-501 Kraków, Poland