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Proton Beam Radiotherapy of Choroidal Melanoma – Practical Aspects

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Summary: Proton beam radiotherapy for choroidal melanoma is a highly effective treatment method that minimizes, but does not eliminate, radiation-related complications. The article covers the practical aspects of the assessment of patient eligibility for treatment, therapy preparation, radiation procedures, and treatment outcomes.

Key words: choroidal melanoma, proton beam radiotherapy.

Uveal melanoma is the most common primary intraocular malignancy in adults. The incidence is higher among white populations and increases at higher latitudes. It exceeds eight cases per million per year in Norway and Denmark but falls below two cases per million per year in Spain and southern Italy [1]. Uveal melanoma is categorized into three subtypes based on anatomical location: choroidal (85–90%), ciliary body (6–9%), and iris (4–6%) [2].

Over the years, numerous methods for treating choroidal melanoma have been developed. The choice of optimal therapy depends on a variety of factors, including the tumor's location and size, coexisting complications, and the patient's overall condition. Treatment methods for choroidal melanoma include radiotherapy, such as brachytherapy (e.g., Ru-106, I-125), proton radiotherapy, and less commonly, external beam radiotherapy (EBRT) or stereotactic radiotherapy, and surgical options encompassing endoresection and exoresection of the tumor, as well as ocular enucleation. Another available treatment method is transpupillary thermotherapy (TTT) using a diode laser [3].

Proton beam radiotherapy has been used at the Department of Ophthalmology and Ocular Oncology in collaboration with the Henryk Niewodniczański Institute of Nuclear Physics of the Polish Academy of Sciences in Krakow (Poland) since January 2011. Since the introduction of this treatment, 369 patients have undergone proton beam irradiation.

Notably, the efficacy of local tumor control after proton beam radiotherapy (approximately 94–96%) and probability of eye preservation (approximately 83–90%) are similar to those achieved with brachytherapy [4–9].

A critical aspect of the treatment process is accurate assessment of patient eligibility. Special consideration is needed when evaluating proton beam radiotherapy as first-line therapy for patients:

- ✓ with tumors located in the papillary, peripapillary, or parapapillary regions, as an alternative to combination treatment (brachytherapy + TTT),
- ✓ with tumors located in close proximity to structures critical for maintaining useful visual acuity, such as the macula and optic nerve (CN II) disc,
- ✓ with tumors whose base dimensions are considerably smaller than the diameter of the applicator with a radioactive source.

Proton beam radiotherapy is a treatment method that requires a longer preparation period compared to brachytherapy, as well as close collaboration between the patient and medical staff during both the preparation phase and the irradiation process itself.

The initial stage of preparation involves a surgical procedure in which 3 to 5 (typically 4) tantalum markers are sutured onto the sclera of the affected eye (Fig. 1). They are crucial for accurately

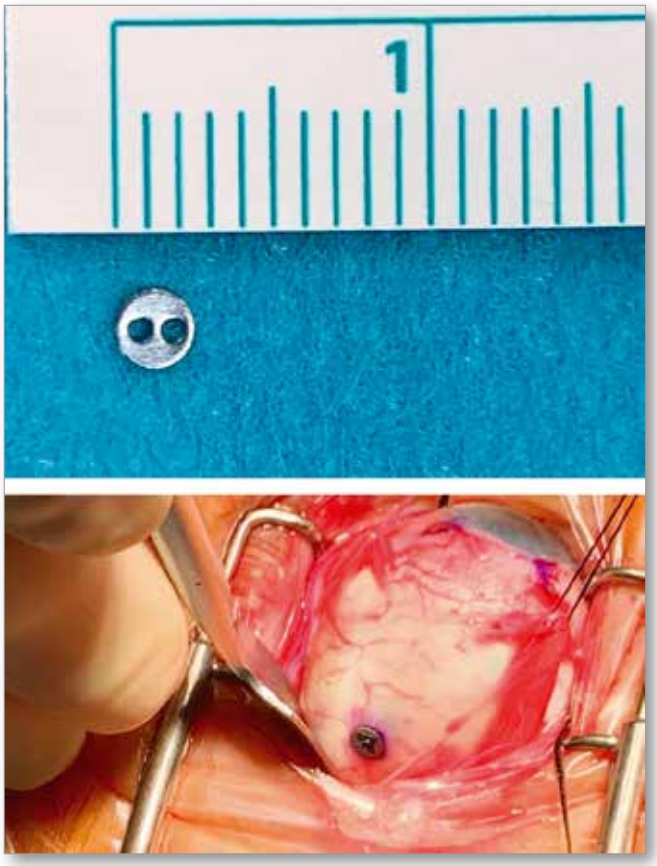

Fig. 1. Tantalum marker before and after suturing to the sclera.

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localizing the tumor in the irradiation plan. As a rule, the markers are not removed after therapy. The patient then undergoes an ultrasound (USG) examination of the eye and magnetic resonance imaging (MRI) of the orbits, following a strictly defined protocol. These imaging procedures are used to create a three-dimensional model of the eye, including the tumor, to facilitate precise therapy planning. If MRI is contraindicated, a computed tomography (CT) scan of the orbits is performed instead. The next step is to prepare a custom thermoplastic face mask and a mouthpiece made of a dental impression material. They are designed to properly immobilize the patient during the irradiation procedure. During a subsequent visit to the Henryk Niewodniczański Institute of Nuclear Physics of the Polish Academy of Sciences, the prepared treatment plan is verified, and trial positioning of the patient is performed (Fig. 2, 3). The actual therapy is conducted on an outpatient basis over the course of the next four days.

The patient is positioned according to the predetermined settings. Each patient has a custom collimator, beam range modulator, and custom eyelid retractors. During irradiation, the patient's eye must remain focused on the light-emitting diode, with real-time verification to ensure proper alignment. The time required

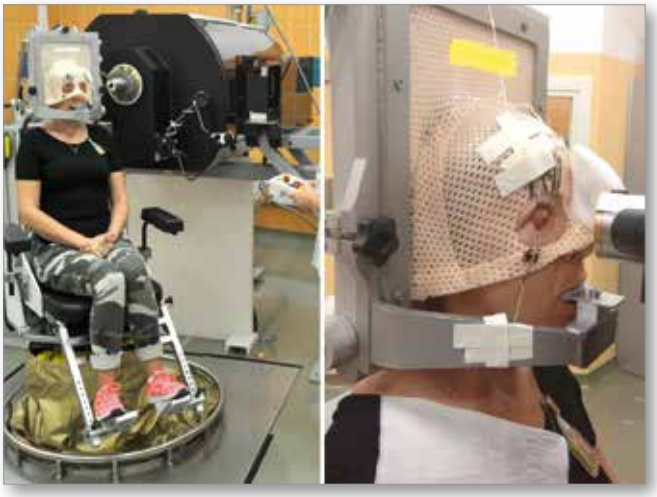

Fig. 2. Patient positioning.

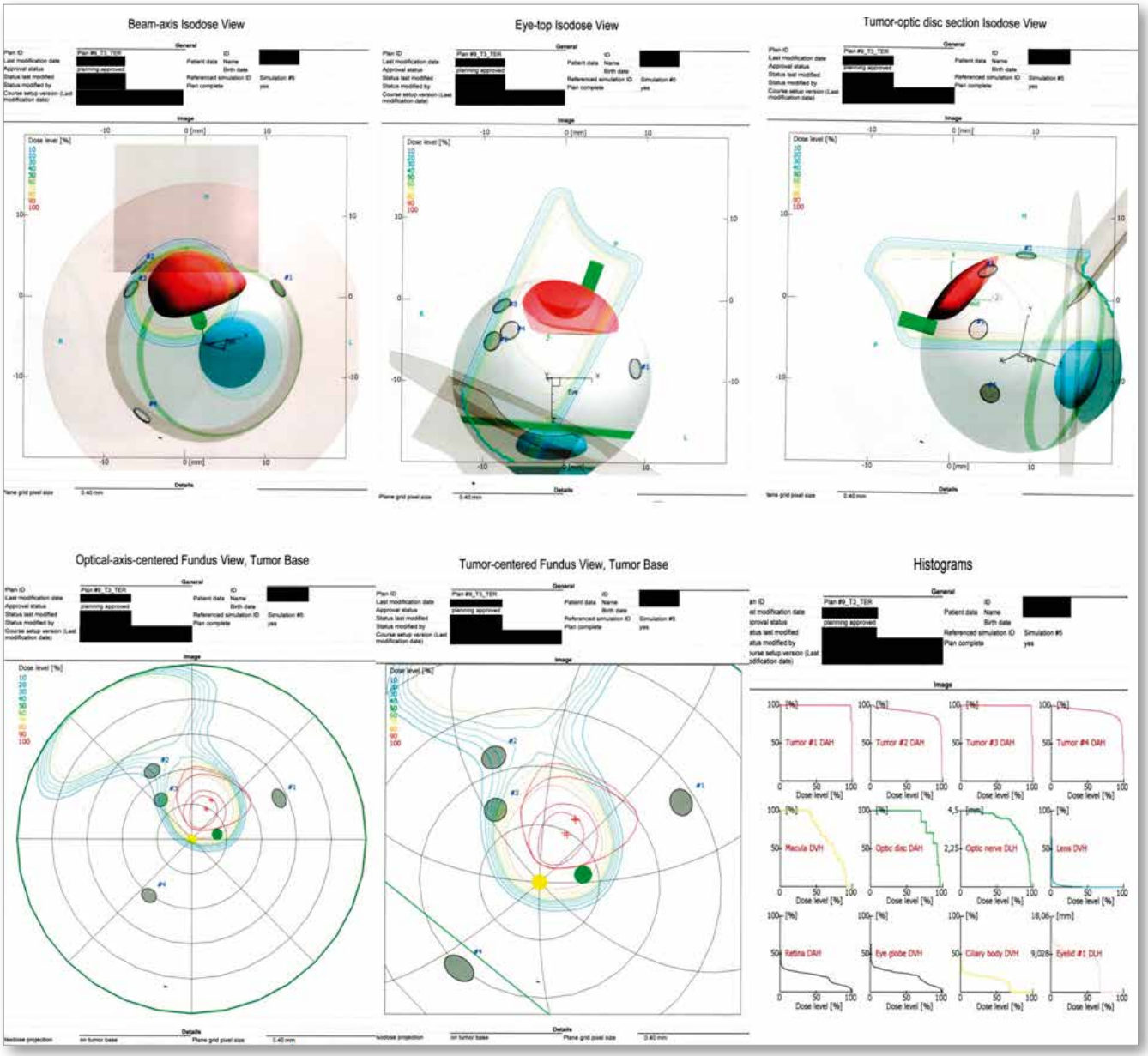

Fig. 3. Simulation and planning of proton beam radiotherapy (selected elements).

to position the patient each day of therapy largely depends on the patient's cooperation with the medical staff. It typically takes about 40-50 minutes, while the proton beam irradiation procedure itself lasts approximately 90 seconds. During radiotherapy, the total dose delivered to the tumor apex is 60 CGE (15 CGE in 4 fractions). Due to the highly individualized nature of the therapy, the irradiated tissue area is restricted to the tumor itself and the necessary margin of surrounding healthy tissue (Fig. 4, 5) [10].

Proton beam radiotherapy for choroidal melanoma can lead to both early and late complications, resulting from the irradiation and necrotic processes occurring within the tumor. In the early post-irradiation period, patients may experience redness and swelling of the conjunctiva, eyelids, and orbital tissues, subconjunctival petechiae, dry eye syndrome, epidermal exfoliation, inflammatory reactions, increased intraocular pressure, worsening retinal detachment associated with the tumor, diplopia, choroidal detachment, and vitreous hemorrhage. Late post-radiation complications include radiation retinopathy and maculopathy, which can be managed with intravitreal or anterior chamber injections of anti-vascular endothelial growth factor (anti-VEGF) inhibitors or steroids. Other complications include radiation neuropathy, secondary glaucoma, complicated cataract, and dry eye syndrome. Additionally, subcutaneous fibrosis, ulceration of eyelid skin, and eyelash loss may develop. It is important to note that the preservation of useful visual acuity after therapy primarily depends on tumor location. Tumors located within 2 DD of the macula or optic nerve are associated with an increased risk of significant visual impairment (visual acuity less than 0.1) [10, 11]. The need for enucleation of an eye previously treated with proton beam radiotherapy is generally due to severe radiation complications or tumor recurrence. The most common complication leading to ocular enucleation is neovascular glaucoma [11–13].

Fig. 4. Choroidal melanoma. A – before (2013) and B – after proton beam radiotherapy (2024).

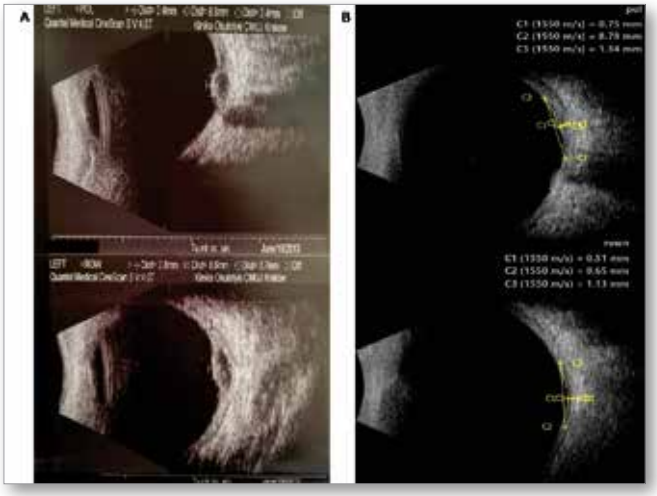

Fig. 5. Choroidal melanoma (on ultraound). A – before (2013) and B – after proton beam radiotherapy (2024).

Each patient treated with proton beam radiotherapy requires ongoing, regular ophthalmological follow-up to assess the tumor's response to treatment and monitor for potential local complications. Additionally, regular oncological follow-up is necessary for the early detection of distant metastases. Follow-up imaging examinations (ultrasound, CT, or MRI) of the abdomen should be performed every six months, along with liver enzyme activity tests every six months, and chest imaging (X-ray or CT) every 12 months.

Proton beam radiotherapy enables individualized and precise tumor irradiation while minimizing the exposure of healthy tissue to radiation. However, it is important to note that this treatment modality requires close collaboration between the patient and the specialist, both during the planning stage and the irradiation process. Additionally, the preparation period for proton beam radiotherapy is longer compared to brachytherapy. The efficacy of both treatment modalities in local tumor control is comparable, and the likelihood of preserving useful visual acuity in the eye treated with proton beam radiotherapy is mainly influenced by tumor location, rather than the type of irradiation used.

Disclosure
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References:

1. Virgili G, Gatta G, Ciccolallo L, et al.: EUROCARE Working Group. *Incidence of uveal melanoma in Europe*. Ophthalmology. 2007 Dec; 114(12): 2309–2315. doi: 10.1016/j.ophtha.2007.01.032. Epub 2007 May 11. PMID: 17498805.
2. Żygulska-Mach H: *Epidemiologia czerniaka oka*. Współczesna Onkologia. 1998; 8: 226–227.
3. Romanowska-Dixon B, Jager MJ, Coupland SE: *Onkologia Okulistyczna*. PZWL Wydawnictwo Lekarskie. Warszawa 2019; 277–300.
4. Mishra KK, Daftari IK: *Proton therapy for the management of uveal melanoma and Rother ocular tumors*. Chin Clin Oncol. 2016; 5(4): 50.
5. Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, et al.: *Treatment of uveal melanoma by accelerated proton beam*. Dev Ophthalmol. 2012; 49: 41–57.
6. Kamran SC, Collier JM, Lane AM, et al.: *Outcomes of proton therapy for the treatment of uveal metastases*. Int J Radiat Oncol Biol Phys. 2014; 90(5): 1044–1050.
7. Damato B, Kacperek A, Chopra M, et al.: *Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience*. Int J Radiat Oncol Biol Phys. 2005; 62(5): 1405–1411.

8. Egger E, Zografos L, Schalenbourg A, et al.: *Eye retention after proton beam radiotherapy for uveal melanoma*. Int J Radiat Oncol Biol Phys. 2003; 55(4): 867–880.

9. Egger E, Zografos L, Munkel G, et al.: *Results of proton radiotherapy for uveal melanomas*. Front Radiat Ther Oncol. 1997; 30: 111–122.

10. Romanowska-Dixon B, Pogrzebielski A, Bogdali A i wsp.: *Radioterapia protonowa czerniaka błony naczyniowej - wstępne wyniki*. Klin Oczna. 2012; 114(3): 173-179.

11. Gragoudas ES: *Proton beam irradiation of uveal melanomas: the first 30 years. The Weisenfeld Lecture*. Invest Ophthalmol Vis Sci. 2006; 47(11): 4666–4673.

12. Hussain RN, Chiu A, Pittam B, et al.: *Proton beam radiotherapy for choroidal and ciliary body melanoma in the UK— national audit of referral patterns of 1084 cases*. Eye. 2022; 37: 1033–1036.

13. Sas-Korczyńska B: [w] *Onkologia Okulistyczna*. PZWL Wydawnictwo Lekarskie. Warszawa 2019; 277–300.

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