

Secondary Glaucoma Following Radiation Therapy for Head and Neck Cancers

Marcin Proniak¹, Łukasz Michalecki^{1,2}, Ewa Mrukwa-Kominek^{1,3}

¹ Kornel Gibiński University Clinical Center, Medical University of Silesia in Katowice, Poland

Head: Professor Dorota Wyględowska-Promieńska, PhD, MD

² Department of Radiotherapy and Oncology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland

Head: Łukasz Michalecki, MD

³ Clinical Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, Poland

Head: Head: Professor Dorota Wyględowska-Promieńska, PhD, MD

Summary:

Radiation therapy is an important treatment modality; however, despite major technological advances in its planning and delivery, it still carries the risk of side effects. Although radiation-induced complications are well documented in the literature, the authors believe that secondary glaucoma associated with head and neck radiation therapy remains notably underrepresented. This serious condition can result not only in irreversible vision loss but may also require enucleation of the affected eye. To reduce such risks, active collaboration between oncologists, radiotherapists, and ophthalmologists is essential. In this article, the authors examine the causes and management of secondary glaucoma following radiation therapy.

Key words:

secondary glaucoma, head and neck radiation therapy, neovascularization, uveitis.

Introduction

Radiation therapy remains a cornerstone in the treatment of head and neck cancers [1–3]. However, despite significant advancements in planning and delivery technologies, it continues to be linked with both early and chronic radiation-induced reactions – adverse effects that may transiently or permanently compromise patients' quality of life [4–7]. The prevention and treatment of radiation-induced reactions often require an interdisciplinary approach. That is why it is so important for clinicians across specialties to understand the pathophysiology of radiation reactions, as well as the diagnostic and therapeutic approaches for managing potential side effects of ionizing radiation treatment.

A rare but potentially serious complication of radiation therapy, which in extreme cases may lead to irreversible blindness, is secondary glaucoma [8, 9]. This article aims to review the pathomechanism and current approaches to the diagnosis, differentiation, prevention, and treatment of secondary glaucoma caused by the effects of ionizing radiation on the organ of vision (Fig. 1).

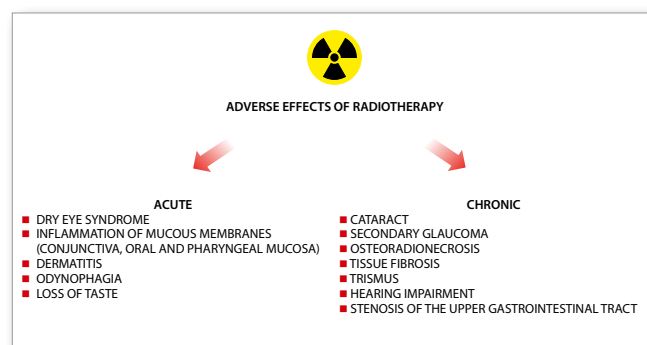


Fig. 1. Side effects of radiotherapy. Acute radiation toxicity occurs usually during radiotherapy session or within 90 days. They are generally reversible, especially if properly handled. Late onset complication occur after 6 months even up to a years after radiotherapy. They can lead to irreversible impairments.

Radiation therapy

Radiation therapy, alongside surgery and systemic treatments such as chemotherapy and immunotherapy, is a fundamental therapeutic modality for cancers of the head and neck. These include carcinomas of the pharynx, oral cavity, nasal cavity, paranasal sinuses, larynx, and salivary glands, as well as, less commonly, lymphomas, sarcomas, and melanomas, including choroidal melanoma. It also plays a key role in treating tumors of the central nervous system – primary and secondary brain neoplasms – as well as non-malignant conditions such as Graves–Basedow ophthalmopathy [10]. It can be used as a primary treatment with curative intent, sometimes in combination with chemotherapy, as an adjuvant therapy following surgery, or, in patients with advanced stages of cancer and/or distant metastases, as palliative treatment. Radiation therapy

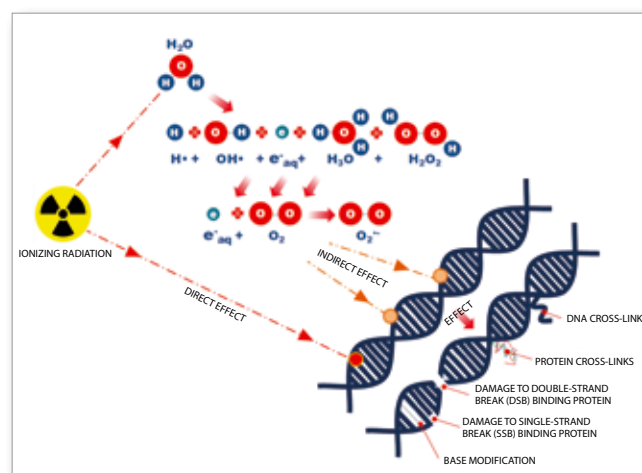


Fig. 2. Mechanism of ionizing radiation. In case of direct effect ionizing radiation directly damage DNA causing growth arrest and apoptosis. Indirectly through radiolysis of water and oxygen forms reactive oxygen species (ROS) which reacting with DNA damages it.

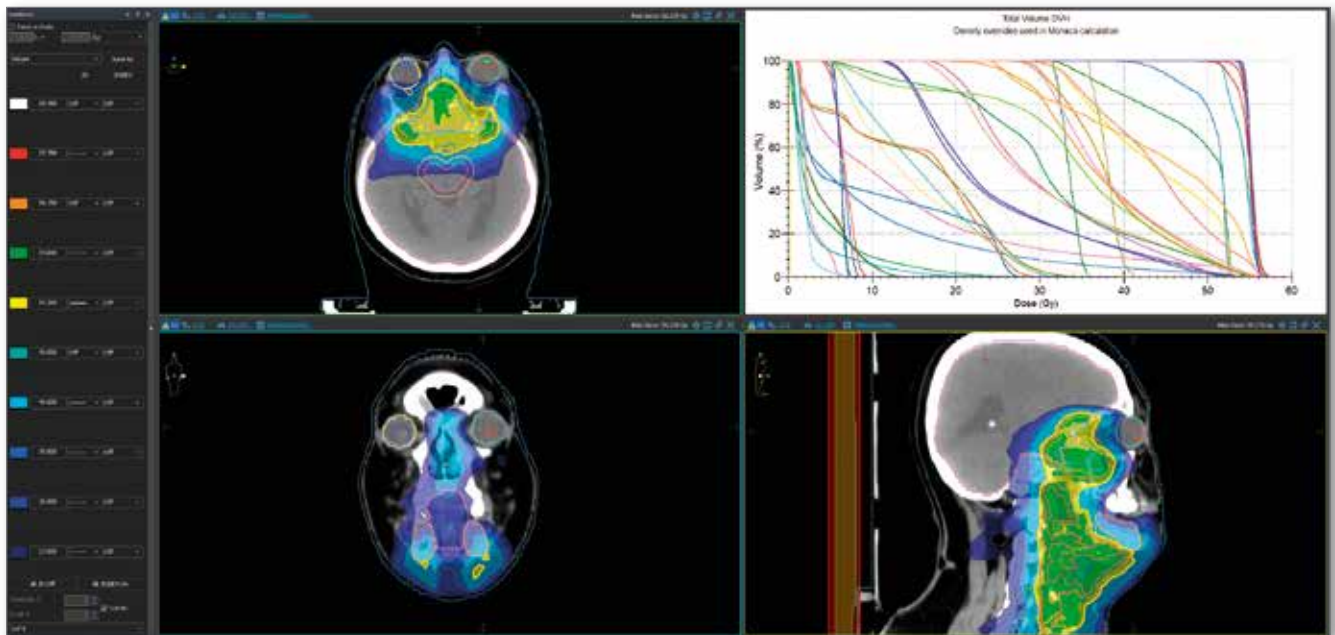


Fig. 3. Example of dose distribution in radiotherapy of nasopharynx and maxilloethmoid complex.

py encompasses modern treatment planning and delivery techniques, such as dynamic methods like IMRT (Intensity-Modulated Radiation Therapy) and VMAT (Volumetric Modulated Arc Therapy), as well as stereotactic techniques and radiosurgery [11]. Thanks to advanced technologies for treatment planning and delivery using modern imaging methods (Image-Guided Radiation Therapy – IGRT) and adaptive techniques, the likelihood of radiation-induced complications is significantly reduced. Other radiation therapy techniques commonly used for ocular tumors include brachytherapy for intraocular tumors and proton therapy. The risk of radiation-induced reactions largely depends on factors such as the total radiation dose, the fractionation schedule, and the dose delivered to specific anatomical structures (Fig. 2, 3) [12–14]. Additionally, comorbidities like diabetes or connective tissue disorders can substantially influence the severity of these reactions.

Glaucoma, that is...

Glaucoma encompasses a group of optic nerve neuropathies associated with remodeling of the connective tissue of the optic nerve head and loss of neural tissue, leading to a distinctive pattern of visual dysfunction, with or without accompanying elevated intraocular pressure (IOP) [15, 16]. Four primary types are distinguished: primary open-angle glaucoma, primary angle-closure glaucoma, secondary glaucoma, and congenital glaucoma. Radiation-associated glaucoma is classified as secondary glaucoma, which may result from fibrosis of the drainage angle or its neovascularization. Puusaari et al. found that the vast majority (84% of cases) were due to neovascularization, 10% resulted from secondary angle closure, and 6% of patients had an open angle [17].

The specific mechanism underlying neovascular glaucoma remains unclear. It is assumed that impaired iris perfusion, for example due to angiopathy of the long posterior ciliary arteries, results in ischemic changes that trigger a cascade of neovascularization [18]. Another possible mechanism is radiation retinopathy, which also promotes the production of angiogenic factors and consequently neovascularization of the drainage angle [19]. Preventing these complications requires a dual approach: lowering and stabilizing IOP while simultaneously interrupting the neovascularization cascade.

Therapeutic management

The first-line approach for managing secondary glaucoma, including cases related to head and neck radiation therapy, is pharmacological treatment. First-line medications include beta-blockers and carbonic anhydrase inhibitors. Whether prostaglandin analogues should also be regarded as first-line therapy remains a matter of ongoing debate. In their mechanism of action, prostaglandin analogues increase the outflow of aqueous humor via the uveoscleral pathway, which may theoretically contribute to the dissemination of metastases in patients with intraocular tumors.

Another method of lowering IOP is cyclodestruction, which reduces the production of aqueous humor. This procedure is typically performed using diode lasers with wavelengths between 693 and 1064 nm, most commonly at 810 nm.

Filtering procedures, which involve creating an additional outflow pathway for aqueous humor from the eyeball and thereby lowering IOP, may pose other challenges. First, due to the risk of metastasis, in cases of intraocular tumor localization, such procedures are recommended only after complete tumor eradication [20]. Second, radiation-induced changes to the conjunctiva – such as fibrosis – can complicate the surgical technique and increase the likelihood of procedural failure. This is related to the difficulty in forming a filtration bleb [20]. However, there are literature reports describing successful stabilization of intraocular pressure after appropriately performed trabeculectomy or Baerveldt valve implantation [20, 21]. When all treatment options fail to stabilize intraocular pressure and the eye has become both blind and painful, enucleation may be necessary [20, 22].

Inflammation of ocular tissues is a relatively common condition following radiation therapy [23]. It may affect the uvea, sclera, episclera, conjunctiva, or cornea. Most often, it presents as mild anterior uveitis accompanied by elevated IOP [24]. In such cases, at the very onset of symptoms, it is recommended to initiate topical treatment not only with IOP-lowering medications, but also with anti-inflammatory agents and cycloplegics. This approach is usually sufficient to both control the inflammatory process and normalize IOP. The next step in lowering IOP and suppressing the inflammatory process is the administration of oral or intravenous medications [23, 25, 26].

It is important to prevent neovascularization, which results from tissue hypoxia and, consequently, induces changes in the drainage angle that underlie reduced aqueous humor outflow. An effective strategy for inhibiting neovascularization involves the use of anti-VEGF agents. Among these agents, bevacizumab is currently the most widely used, typically given as a series of three monthly intravitreal injections [27]. Adjunctive laser therapy – (Panretinal Photocoagulation – PRP) – should also be considered. By destroying areas lacking perfusion, this procedure eliminates angiogenic stimulation and demonstrates even greater efficacy. This is particularly relevant in cases where intravitreal injections cannot be administered – for instance, due to the patient's local or systemic condition. Panretinal photocoagulation also helps lower the risk of potential evisceration of the eye [27].

Conclusions

Glaucoma is a rare but serious complication of radiation therapy, with the potential to cause irreversible blindness. In patients developing this complication, it is essential to reduce intraocular pressure and inhibit neovascularization, while controlling any associated inflammatory response. To mitigate the risk of secondary glaucoma, it is considered good practice to perform ophthalmologic examinations in all patients exposed to ionizing radiation involving the eye, periorbital tissues, head, or neck – both before and after radiation therapy. This approach helps prevent complications and enables timely implementation of appropriate therapeutic interventions.

Given the rising incidence of head and neck cancers and the growing number of patients receiving radiation therapy in these regions, it is essential that ophthalmologists, oncologists, and radiotherapists remain vigilant about the risk of secondary glaucoma – a potential serious complication that may lead to irreversible blindness.

References:

1. Barton MB, Jacob S, Shafiq J, et al.: *Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012*. *Radiation Oncol*. 2014; 112: 140–144.
2. Saloura V, Langerman A, Rudra S, et al.: *Multidisciplinary care of the patient with head and neck cancer*. *Surg Oncol Clin N Am*. 2013; 22: 179–215.
3. van der Molen L, van Rossum MA, Burkhead LM, et al.: *Functional outcomes and rehabilitation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review*. *Eur Arch Otorhinolaryngol*. 2009; 266: 889–900.
4. Filarska D, Czyżewska K: *Uszkodzenie narządu wzroku po radioterapii – przegląd literatury*. *Współczesna Onkologia*. 2000; vol. 4; 3: 109–110.
5. Zemba M, Dumitrescu OM, Gheorghe AG, et al.: *Ocular Complications of Radiotherapy in Uveal Melanoma*. *Cancers*. 2023; 15(2): 333.
6. Wen JC, Oliver S, McCannel TA: *Ocular complications following I-125 brachytherapy for choroidal melanoma*. *Eye*. 2009; 23: 1254–1268.
7. Groenewald C, Konstantinidis L, Damato B: *Effects of radiotherapy on uveal melanomas and adjacent tissues*. *Eye*. 2012; 27: 163–171.
8. Gopalakrishna M, Srinivasan K, Rengaraj V: *Radiation-induced neovascular glaucoma: A devastating disease*. *J Can Res Ther*. 2020; 16: S213–216.
9. Kim EA, Salazar D, McCannel CA, et al.: *Glaucoma After Iodine-125 Brachytherapy for Uveal Melanoma: Incidence and Risk Factors*. *J Glaucoma*. 2020 Jan; 29(1): 1–10.
10. Takeda A, Shigematsu N, Suzuki S, et al.: *Late retinal complications of radiation therapy for nasal and paranasal malignancies: relationship between irradiated-dose area and severity*. *Int J Radiat Oncol Biol Phys*. 1999; 44: 599–605.
11. Alterio D, Marvasoa G, Ferrari A, et al.: *Modern radiotherapy for head and neck cancer*. *Seminars in Oncology*. 2019 June; Volume 46, Issue 3.
12. Joiner MC, van der Kogel A: *Basic Clinical Radiobiology*. CRC Press, 2018.
13. Hall EJ, Giaccia AJ: *Radiobiology for the Radiologist*. Wolters Kluwer, 2018.
14. Ziolkowska E, Zarzycka M, Meller A, et al.: *Powikłania oczne po radioterapii nowotworów regionu głowy i szyi – przegląd piśmiennictwa*. *Współczesna Onkologia*. 2009; vol. 13; 5: 251–254.
15. Foster PJ, Buhmann R, Quigley HA, et al.: *The definition and classification of glaucoma in prevalence surveys*. *Br J Ophthalmol*. 2002; 86 (2): 238–242, doi: 10.1136/bjo.86.2.238.
16. BCSC 10 Jaskra Edra Urban & Partner.
17. Puusaari I, Heikkonen J, Kivelä T: *Ocular complications after iodine brachytherapy for large uveal melanomas*. *Ophthalmology*. 2004; 111: 1768–1777.
18. Detorakis ET, Engstrom RE, Wallace R, et al.: *Iris and anterior chamber angle neovascularization after iodine 125 brachytherapy for uveal melanoma*. *Ophthalmology*. 2005; 112: 505–510.
19. Brour J, Desjardins L, Lehoang P, et al.: *Sympathetic Ophthalmia after Proton Beam Irradiation for Choroidal Melanoma*. *Ocul Immunol Inflamm*. 2012; 20: 273–276.
20. Riechardt AI, Cordini D, Rehak M, et al.: *Trabeculectomy in patients with uveal melanoma after proton beam therapy*. *Graefes Arch Clin Exp Ophthalmol*. 2016; 254: 1379–1385.
21. Sharkawi E, Oleszczuk JD, Bergin C, et al.: *Baerveldt shunts in the treatment of glaucoma secondary to anterior uveal melanoma and proton beam radiotherapy*. *Br J Ophthalmol*. 2012; 96: 1104–1107.
22. Seibel I, Riechardt AI, Heufelder J, et al.: *Adjuvant Ab Interno Tumor Treatment After Proton Beam Irradiation*. *Am J Ophthalmol*. 2017; 178: 94–100.
23. Lumbroso L, Desjardins L, Levy C, et al.: *Intraocular Inflammation after Proton Beam Irradiation for Uveal Melanoma*. *Br J Ophthalmol*. 2001; 85: 1305–1308.
24. Fries PD, Char DH, Crawford JB, et al.: *Sympathetic ophthalmia complicating helium ion irradiation of a choroidal melanoma*. *Arch Ophthalmol*. 1987; 105: 1561±4. = 1561–1564.
25. 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.
26. Hager A, Meissner F, Riechardt AI, et al.: *Breakdown of the Blood-Eye Barrier in Choroidal Melanoma after Proton Beam Radiotherapy*. *Graefes Arch Clin Exp Ophthalmol*. 2019; 257: 2323–2328.
27. Mahdjoubi A, Najean M, Lemaitre S, et al.: *Intravitreal bevacizumab for neovascular glaucoma in uveal melanoma treated by proton beam therapy*. *Graefes Arch Clin Exp Ophthalmol*. 2017; 256: 411–420.

Reprint requests to:

Marcin Proniak, MD (e-mail: marcinproniak@gmail.com)
Kornel Gibiński University Clinical Center, Medical University of Silesia
in Katowice, Poland
Ceglana 35, 40-514 Katowice