



RESEARCH ARTICLE

# Treatment Paradigms in Radiation Maculopathy Treatment: What's Next?

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## ABSTRACT

Radiation is the most common life and sight-sparing treatment for eye cancer patients. However, it can subsequently lead to a dose-dependent, progressive radiation vasculopathy, which results in retinopathy- or optic neuropathy-related vision loss. Before the advent of intravitreal drug therapy, laser destruction of the ischemic retina was found to be effective for select patients. However, in 2006, the anti-vascular endothelial growth factor bevacizumab was found to trigger regression and suppress radiation maculopathy and optic neuropathy. Anti-vascular endothelial growth factor drugs were administered initially to forestall vision loss in patients with clinically significant disease. Advancements in retinal imaging and a better understanding of their capabilities resulted in earlier intervention with anti-vascular endothelial growth factor treatment. Still, not all the radiation damage to the retina was reversible. To prevent this irreversible injury, periodic anti-vascular endothelial growth factor therapy was given to those patients at the highest risk of developing radiation-related maculopathy within six months of high-dose foveal plaque radiation therapy. This research found that treating patients before clinically evident radiation maculopathy prevented or delayed the onset of radiation maculopathy with preservation of vision. Other strategies to prevent vision loss due to progressive, recalcitrant retinopathy have included the off-label use of alternative therapeutic agents and polypharmacy with intravitreal steroids. These therapeutic agents should be evaluated in protocols where intervention can be guided by optical coherence tomography angiography as subclinical obliterated retinal microangiopathy appears to start at the time of or soon after ocular irradiation. Treatment strategies have evolved, especially as our understanding of the condition has improved. We propose that future protocols take advantage of new therapies, use advances in retinal imaging, and employ novel technologies to establish optimal treatment regimens. Keywords: radiation retinopathy, radiation optic neuropathy, radiation maculopathy, anti-VEGF, drug, radiation dose, intravitreal, bevacizumab, ranibizumab, steroid.

## Introduction

Radiation maculopathy (RM) and optic neuropathy (RON) are vision-threatening complications of radiation therapy used for ocular, periorbital, orbital, and sinus tumors.<sup>1</sup> Radiation therapy has primarily replaced enucleation for patients with intraocular melanoma, resulting in significant quality-of-life improvements by conserving both the eye and useful vision.<sup>2-7</sup> While radiation has changed how ocular melanoma is treated, it can cause damage to surrounding structures.<sup>8-12</sup> Common complications include dry eye, cataracts, radiation maculopathy, and radiation optic neuropathy.<sup>1,13,14</sup> Of these complications, radiation maculopathy is the most frequent cause of irreversible vision loss in eyes treated with radiation and most often results following the treatment of choroidal melanoma.<sup>4,8,15-19</sup>

Radiation maculopathy is a result of radiation-induced damage to the retinal microvasculature. Radiation destroys vascular pericytes, leading to leakage of serum and inflammatory components into the retina. Early clinical findings include retinal hemorrhages, cotton wool spots, and macular edema. Later findings, such as capillary dropout, retinal ischemia, and intraretinal neovascular microangiopathy, are best identified on fluorescein angiography (FA).<sup>8,10-12</sup> This pathway is similar to the underlying etiology of diabetic retinopathy (DR). Unsurprisingly, patients with radiation maculopathy present similarly to those with diabetic retinopathy, as both conditions are characterized by delayed onset vascular incompetence leading to retinal edema, exudation, and end-stage ischemia with vision loss (Figure 1). Clinically, both are notable for decreased visual acuity and retinal changes, including microaneurysms (MA's), retinal hemorrhages (RH), exudates, and cotton-wool spots (CWS). Though the vascular changes are

similar, radiation optic neuropathy often presents as disc edema or neovascularization.

Innovations in retinal imaging and therapeutics for radiation maculopathy and diabetic retinopathy have advanced in parallel. For both diseases, laser photocoagulation, intravitreal anti-vascular endothelial growth factor (VEGF), and steroid treatments have been used to suppress VEGF. Thus, a historical perspective is essential in mapping out future research goals and understanding shifts in treatment paradigms. For diabetic retinopathy, advancements in retinal imaging from FA to optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) have helped establish diabetic retinopathy treatment protocols. Though radiation maculopathy tends to be a more fulminant disease, eye cancer and retinal specialists should consider these parallels when developing protocols for the treatment of radiation maculopathy and radiation optic neuropathy.

We propose that the treatment of radiation maculopathy and radiation optic neuropathy mimic the protocols used for diabetic retinopathy. Anti-VEGF therapies have already been widely adopted as a first-line treatment option, and this shift was driven by the recognition that both conditions share similar pathophysiological features, such as increased VEGF levels leading to macular edema and capillary non-perfusion. As such, the treatment of radiation maculopathy and radiation optic neuropathy should continue to evolve, with a strong emphasis on early intervention and the use of newer anti-VEGF therapies closely resembling the treatment protocols for diabetic retinopathy. We postulate that prospective randomized or extensive registry studies will support initial data that such treatment protocols will improve visual outcomes and quality of life for patients with this condition.

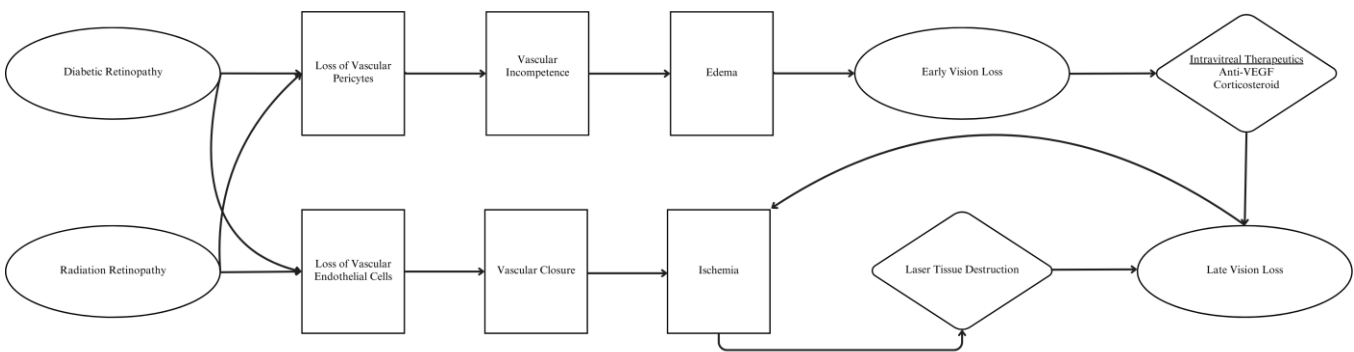


Figure 1. Pathophysiological mechanisms of ionizing radiation-related vs diabetic-related retinal vasculopathy leading to vision loss.

## Methods

A literature search was last conducted in PubMed and the Cochrane Library databases on 01 July 2024 using the following MeSH terms: radiation retinopathy, radiation maculopathy, radiation optic neuropathy, treatment, light coagulation, intraocular, and anti-VEGF agents. The search used the following text terms: radiation retinopathy, radiation maculopathy, radiation optic neuropathy, light coagulation, photocoagulation, and intraocular injections. Articles were limited to those in English. Relevant articles were pursued, and the initial search expanded using the “pearl-growing” technique. The investigators reviewed articles. The lead investigator performed a full-text review of the articles included, and

after the full-text review, an in-depth analysis of the remaining articles was conducted.

## Progression of Radiation Maculopathy and Radiation Optic Neuropathy

The speed of onset of clinically detectable radiation-induced vascular incompetence is proportional to radiation dose and dose rate.<sup>3,8,20</sup> Typically, the first evidence of radiation maculopathy is macular edema, best measured by OCT or radiation optic neuropathy with disc edema-associated loss of the optic cup.<sup>21</sup> Recent research reveals that early microvascular changes can be found on OCTA. OCT findings have been detected before other clinical signs, including retinal hemorrhages

and cotton-wool spots. Late or end-stage radiation maculopathy is characterized by capillary dropout and foveal avascular zone enlargement, best seen on fluorescein angiography.<sup>22</sup> Late-stage radiation optic neuropathy is characterized by disc pallor, fluorescein leakage, and vision loss.<sup>21</sup>

Shields *et al.* found early evidence of superficial and deep capillary plexus dropout on OCTA in 65 eyes after plaque radiotherapy of choroidal melanoma patients without clinical evidence of radiation maculopathy.<sup>23</sup> This finding was confirmed by Fam *et al.* after slotted plaque brachytherapy.<sup>24</sup> Highlighting the limitations of ophthalmoscopy for the diagnosis of radiation maculopathy, Horgan *et al.* used OCT to assess the onset of radiation macular edema in 135 patients after relatively high-dose<sup>125I</sup> plaque radiotherapy plus transpupillary thermotherapy for choroidal melanoma. Horgan found a progressive incidence of pre-clinical radiation-induced macular edema as it occurred in 17% of patients by six months, 40% by one year, and 61% by two years. In that series, clinical findings of radiation maculopathy were detected much later, at an average of 17 months, and 38% of cases were complicated by neovascularization, vitreous hemorrhage, and tractional retinal detachments.<sup>25,26</sup>

## First Efforts at Control of Radiation Maculopathy

Before the advent of intravitreal anti-VEGF therapy, sector laser photocoagulation, including demarcation occlusion of the tumor's circulation and/or a grid pattern laser to extrafoveal areas of the ischemic retina, was initially employed to prevent or delay the progression of radiation maculopathy.<sup>27</sup> This concept resembled laser treatment of branch vein occlusions and diabetic retinopathy.<sup>28–33</sup> As this was before the advent of OCT, clinical examination and fluorescein angiography were used to demonstrate the efficacy of laser treatment. Materin also found that laser photocoagulation reduced circulation within irradiated choroidal melanomas and minimized hypoxia in tissues downstream.<sup>27,34</sup> Thus, laser reduced VEGF production, not only from the tumor itself but also from nearby irradiated retinal ischemic tissue.<sup>35,36</sup> While this was the only method available at the time to reduce VEGF levels, photocoagulation was not ideal for those tumors near, touching, or located beneath the fovea and adjacent to the optic disc due to risks for acute vision loss.<sup>27,37</sup>

## Evolution of Case Selection

Anti-vascular endothelial growth factor therapy provided an exciting solution to this treatment dilemma. Supported by the macular edema measurement capabilities of OCT imaging, intravitreal anti-VEGF medications were initially offered to patients with RM-associated vision loss who could not be treated with laser photocoagulation.<sup>38,39</sup> This promising new therapeutic demonstrated clinical results with reductions in CWS, RH, and macular edema, preserving vision.<sup>38,40</sup> As the safety profile was established, anti-VEGF treatment was offered to progressively less advanced radiation maculopathy cases and mirrored ongoing treatment regimens for diabetic retinopathy and macular degeneration. For example, anti-VEGF injections were

initially reserved for radiation maculopathy patients with vision loss, then for those with metamorphopsia, and later for eyes with CWS, RH, or macular edema (ME) without metamorphopsia or vision loss.<sup>41–43</sup> All these cases demonstrated clinical signs or evidence of radiation maculopathy on OCT or FA. However, it became evident that despite the drug-induced resolution of these clinical and OCT findings, persistent retinal vascular damage—and vision loss—remained.<sup>41</sup>

Optical coherence tomography angiography has recently demonstrated early subclinical retinal microangiopathy and that vascular compromise occurred before otherwise measurable radiation maculopathy, such as leakage, edema, hemorrhage, nonperfusion, and neovascularization.<sup>23,24,44–47</sup> Powell and Finger showed that a dose-dependent, ischemic radiation vasculopathy begins at or soon after irradiation but only becomes clinically evident when it causes retinal edema, ischemia, and vision loss.<sup>22</sup> An ever-increasing body of evidence supports targeting this subclinical phase with intravitreal anti-VEGF treatment, particularly in those patients at the highest risk for vision loss due to radiation maculopathy.<sup>48–51</sup> This was confirmed most recently in a meta-analysis analyzing four studies involving 2109 patients by Victor *et al.*, demonstrating that prophylactic anti-VEGF therapy prevented high-risk patients from developing poor visual acuity (20/200 or worse) by 50%. In addition, there were significant reductions in radiation maculopathy, radiation optic neuropathy, and loss of visual acuity.<sup>52</sup>

## Paradigm Shift: Resemblance to Diabetic Retinopathy Treatment Protocols

As retinal imaging advances, the future treatment of radiation maculopathy and radiation optic neuropathy has multiple directions: new pharmacologic agents, combination therapies, gene therapy, radiation protectants, stem cell therapy, new drug delivery systems, and personalized medicine.

Traditional treatment approaches to radiation maculopathy and radiation optic neuropathy involve observation of early or mild cases, laser photocoagulation, intravitreal steroids, and anti-VEGF therapy. The first reports of anti-VEGF treatment for radiation maculopathy and radiation optic neuropathy were published in 2007.<sup>38,40</sup> At that time, bevacizumab and ranibizumab were the only commercially available drugs. Since then, aflibercept, ranibizumab, and brolucizumab have all been used to treat radiation retinopathy.<sup>43,53,54</sup> Additional variations include higher-monthly dose therapies utilizing bevacizumab, ranibizumab, and aflibercept, as well as adjuvant intravitreal steroid polypharmacy, which have emerged. Such polypharmacy has been used for cases recalcitrant to anti-VEGF therapy alone. Steroid medications have included triamcinolone acetonide, dexamethasone, and fluocinolone acetonide. Each differs in risk for acute obscuration of vision, duration of action, and cost.

As the treatment of radiation maculopathy and radiation optic neuropathy increasingly paralleled the protocols used for diabetic retinopathy, particularly with the adoption of anti-VEGF therapies as a first-line treatment

option, we propose a paradigm shift to include early detection with newer retinal imaging modalities and intervention with proactive treatment initiation rather than a wait-and-see approach, regular intravitreal anti-VEGF injections with formalized protocols that involve early monthly injections initially with a treat-and-extend approach based on the patient's response, and combination therapy or the use of newer therapeutic agents in such protocols.

Amongst anti-VEGF drugs, high-dose aflibercept is a promising therapeutic option deserving of additional study, particularly in refractory or high-risk cases. Increasing anti-VEGF strength had a beneficial effect in previously unresponsive cases of RM treated with intravitreal ranibizumab (2.0 mg) and bevacizumab (2.0, 2.5, or 3.0 mg). Although high-dose therapy increased drug volume, it resulted in significant reductions in macular edema and maintained or improved best-corrected visual acuity.<sup>54</sup> Aflibercept 8 mg is an anti-VEGF inhibitor that blocks vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PGF), thereby reducing angiogenesis and vascular permeability. The United States Food and Drug Administration (FDA) approved the use of this high-dose formulation of aflibercept in August 2023 for the treatment of diabetic macular edema (recommended dose of 8 mg administered intravitreally every 8 to 16 weeks, after three monthly loading doses) and diabetic retinopathy (recommended dose every 8 to 12 weeks after three monthly loading doses). These recommendations were based on the randomized, double-masked phase 2/3 trial where the 8 mg formulation demonstrated clinically equivalent vision gains to aflibercept 2 mg and that these gains were maintained with fewer injections. In this non-inferiority study, patients receiving aflibercept 8 mg were initially randomized to either 12- or 16-week dosing intervals after three initial monthly doses, compared to an 8-week dosing regimen for aflibercept 2 mg after five initial monthly doses.<sup>55</sup>

In the treatment of radiation retinopathy, aflibercept 2mg/0.05mL injection has been shown in one prospective study by Murry *et al.* to help maintain vision in patients with radiation maculopathy.<sup>56</sup> In this prospective study, patients were randomly assigned to receive aflibercept 2.0 mg/0.05 mL injections on a fixed 6-week schedule or under a treat-and-extend protocol. In this paper, the authors note that they initially hoped that the treat-and-extend arm would allow for fewer intravitreal injections during the study, but almost all patients required treatment every six weeks. Aflibercept 8 mg may help minimize the number of injections needed while maintaining visual benefit.

Steroids have been a helpful treatment adjunct to anti-VEGF therapy. In patients who did not respond to maximum doses of anti-VEGF medications, Kaplan *et al.* demonstrated the efficacy of adding 4 mg of triamcinolone acetonide to treatment with anti-VEGF medicines. Vision stabilized or improved in 100% of patients at three months, 88% at six months, 88% at nine months, and 75% at 12 months.<sup>57</sup> If the primary goal is to decrease the VEGF drive and inflammatory cascade that begins at the time of treatment, adjunctive steroids

and aflibercept 8 mg should be considered in future treatment protocols.

Faricimab is also deserving of further investigation. Faricimab is a bispecific antibody inhibiting VEGF-A and angiopoietin-2 (Ang-2). It promotes vascular stability by inhibiting Ang-2, which destabilizes blood vessels and exacerbates inflammation. The FDA approved the use of this medication in January 2022 for diabetic macular edema, recommending 6 mg intravitreal injections every four weeks for the first four doses, followed by as-needed dosing. These approvals were based on encouraging results across two identical Phase 3 studies in diabetic macular edema (YOSEMITE and RHINE), which showed that after four initial monthly doses, patients treated with faricimab given at intervals of up to 4 months achieved non-inferior vision gains versus aflibercept given every two months in the first year.<sup>58</sup> Applying our knowledge of the commonalities in the pathophysiology of diabetic retinopathy and radiation maculopathy, we have had preliminary success in using faricimab to successfully treat refractory radiation maculopathy in two patients with persistent macular edema minimally responsive to aflibercept 2mg/0.05mL. Both patients experienced improvements in their visual acuity along with improvement of macular edema both clinically and on imaging. Faricimab may be particularly applicable in refractory cases that require treatment with both corticosteroids and anti-VEGF agents.

## Conclusion

We have presented the microvascular and anatomic pathophysiology of radiation maculopathy and radiation optic neuropathy and compared their current treatment strategies with diabetic retinopathy, given the similarities in their underlying pathophysiology. Diabetic retinopathy has benefited from organized prospective, randomized studies. We postulate that due to their shared vascular findings, those who treat radiation maculopathy and radiation optic neuropathy can benefit from known diabetic retinopathy experience and give an example framework for future studies (Figure 2). We also reviewed the evolution of radiation maculopathy treatments, revealing that at first, laser photocoagulation was used, albeit unknowingly, to reduce VEGF production from choroidal melanomas and radiation-induced ischemic retina, after which it was largely abandoned with the advent of tissue-sparing intravitreal anti-VEGF therapy. During this time, fundus photography, fluorescein angiography, and, most importantly, OCT allowed for periodic assessments of macular thickness and provided a means to quantify the need for periodic treatment. In its many forms, anti-VEGF therapy has been found to prevent or delay vision loss due to radiation maculopathy and optic neuropathy. However, we have also learned that radiation vasculopathy starts at the time of ocular irradiation. Its onset and severity depend on radiation dose to the macula and optic nerve. Both radiation maculopathy and diabetic retinopathy are chronic progressive disease processes that often require continuous periodic treatment.

Advances in retinal imaging will continue to guide the use of newer therapeutic agents in future treatment and research protocols for radiation-related maculopathy



and optic neuropathy. For example, OCTA, which can detect subclinical radiation vasculopathy, should be used in future studies to formalize anti-VEGF treatment protocols to prevent vision-threatening radiation maculopathy.<sup>23,44,45</sup> Like the more evolved study-based protocols used for treating diabetic retinopathy, the radiation maculopathy literature supports the need for prospective, randomized clinical trials or retrospective multicenter registries. However, unlike diabetic retinopathy, such studies are complicated, using many different radiation sources and methods.<sup>1</sup> Prospective randomized or extensive registry studies are needed to test our early findings that intravitreal anti-VEGF injections may prevent or delay radiation maculopathy and optic neuropathy-related vision loss and can be used to establish ideal treatment regimens.<sup>22</sup> Such data will support the economic commitment of the government, insurers, and patients to radiation maculopathy treatment. It will also allow for the personalization of treatment, improve outcomes, and save vision worldwide.

**Conflict of Interest:** Dr. Finger holds United States Patent #7,553,486, June 30<sup>th</sup>, 2009, titled, “Anti-VEGF Treatment for Radiation Induced Vasculopathy.”

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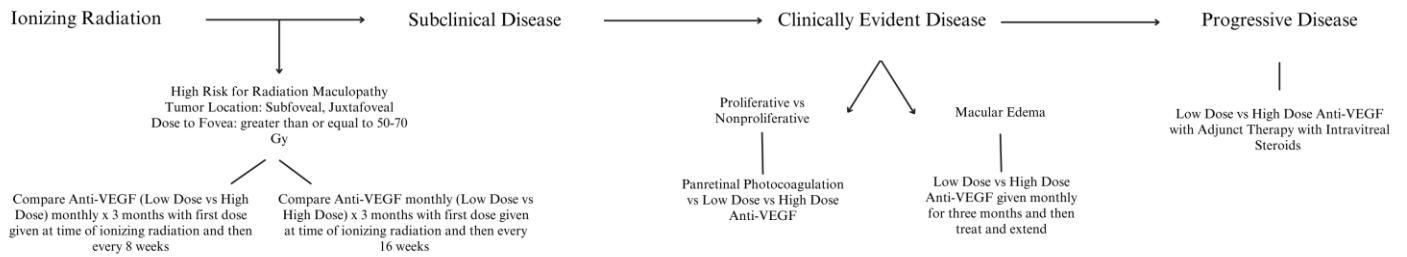


Figure 2. Possible framework for a prospective randomized clinical trials or retrospective multi-center registry to determine the ideal initiation of treatment and dosing patterns in the treatment of radiation retinopathy. High Dose Anti-VEGF would include newer therapeutics such as aflibercept 8 mg vs Low Dose Anti-VEGF which would refer to current treatment regimens using therapeutics such as aflibercept 2 mg.

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