Update on diagnosis and management of radiation retinopathy

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Purpose of review
Radiation retinopathy is a vision-threatening complication of radiotherapy involving the eye or surrounding structures. This review aims to summarize recent advances in understanding the incidence, risk factors, pathophysiology, and utilization of new diagnostic imaging tools for radiation retinopathy. It will also focus on the current prophylaxis approaches to prevent or delay the development of radiation-related side effects and treatment strategies once radiation retinopathy occurs.

Recent findings
The incidence of radiation retinopathy is influenced by radiation dose, fractionation schedule, and patient-specific factors such as diabetes mellitus and hypertension. Advances in imaging techniques, including optical coherence tomography angiography (OCTA) and ultra-widefield fluorescein angiography (UWFA), have enhanced early detection by identifying subclinical retinal changes. Novel insights into pathophysiology suggest a role for endothelial damage, inflammation, and oxidative stress in disease progression. Prophylactic approaches, such as intravitreal antivascular endothelial growth factor (anti-VEGF) agents, have shown promise in reducing the onset of retinopathy in high-risk patients. Therapeutic options, including intravitreal anti-VEGF and corticosteroids, have demonstrated efficacy in managing macular edema and preserving vision. However, the outcomes remain variable, necessitating personalized treatment strategies. To address some of these unanswered questions, the Diabetic Retinopathy Clinical Research Network (DRCR) Protocol AL is currently enrolling patients and preparing to analyze the long-term effects of treating patients prophylactically with intravitreal faricimab or the 0.19 mg fluocinolone acetonide implant compared to observation, to identify which patients will benefit from which specific regimen, therefore moving towards a personalized approach for this condition as well.

Summary
Radiation retinopathy remains a significant challenge in ophthalmology. Early recognition through advanced imaging and tailored interventions, including prophylaxis and treatment, are crucial for optimizing visual outcomes. Further research into underlying mechanisms and novel therapies is essential to reduce the burden of this condition and improve patient quality of life.

Keywords
antivascular endothelial growth factors, corticosteroids, endothelial injury, macular edema, ocular oncology, oxidative stress, radiation maculopathy, radiation retinopathy, radiotherapy, uveal melanoma

INTRODUCTION

Severe ocular disease including radiation retinopathy and optic neuropathy can occur when patients are exposed to ionizing radiation through occupational sources, environmental hazards, or therapeutic treatments [1,2]. Radiation retinopathy often occurs after radiation treatment for ocular tumors or periocular head and neck malignancies [1,2]. It may result in progressive vision loss secondary to microvascular damage and retinal ischemia induced by direct endothelial damage from free radicals and oxidative stress. Radiation retinopathy can lead to several complications, including retinal ischemia, retinal neovascularization, vitreous hemorrhage, and neovascular glaucoma among others [3]. Numerous factors must be considered when gauging the risk of developing radiation retinopathy as the disease is multifactorial [4–6]. Furthermore, patients

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KEY POINTS

- Radiation retinopathy is a multifactorial disease that develops after exposure to ionizing radiation. Several factors contribute to its development and severity including the type of radiation, total dose of radiation administered, dose fractionation, tumor location, tumor size, and the presence of other systemic or ocular comorbidities.
- Several ancillary imaging modalities, including both noninvasive such as optical coherence tomography (OCT) and OCT angiography and invasive such as fluorescein angiography, help in early detection of subclinical findings of radiation retinopathy as well as its late complications including neovascularization.
- There is no universally accepted prophylactic regimen to prevent or delay visually significant radiation side effects to the retina, but the main efforts should be made in delivering the lowest effective dose of radiation in a targeted way.
- Prophylactic procedures such as targeted sectoral laser photocoagulation, intravitreal injection of antivascular endothelial growth factors (VEGF), or corticosteroids, are commonly used and have demonstrated efficacy in reducing the likelihood of developing radiation retinopathy and reducing the risk of developing vision worse than 20/200.
- Treatment of noncomplicated radiation retinopathy includes injections of anti-VEGF and corticosteroids with variable frequency, as well as retinal laser photocoagulation. Complications such as persistent vitreous hemorrhage, traction retinal detachment, and neovascular glaucoma often warrant surgical intervention.

should be monitored for years after radiation exposure to ensure early detection and treatment of the retinopathy.

INCIDENCE AND RISK FACTORS

Intraocular malignancy was historically treated with enucleation. However, with the advent of radiation therapy for benign and malignant primary and metastatic tumors and the Collaborative Ocular Melanoma Study demonstrating similar survival rates for radiation versus enucleation for patients with uveal melanoma, there has been an increase in the utilization of radiation therapy [1]. This has led to an increase in the prevalence of radiation retinopathy, which varies significantly in the literature. A recent meta-analysis of 29 studies and 2458 patients with head and neck cancer suggests that the prevalence of radiation retinopathy is 6% in all patients exposed to radiation therapy, but some of the included studies found the prevalence to be as high as 70% [2]. Differences in prevalence are likely multifactorial, which should be considered when evaluating disease risk. Factors that contribute to the development of retinopathy include the total dose of radiation administered, dose fractionation, type of radiation, tumor location, tumor size, previous or concomitant chemotherapy, and the presence of other vascular comorbidities such as hypertension, diabetes mellitus, sickle cell disease, and retinal vein occlusion [3–6].

The dose-dependent nature of radiation retinopathy is extremely important when considering disease risk. Tumors vary in radiation sensitivity, with those that are more resistant requiring higher doses of radiation, ultimately increasing the risk of radiation-related side effects [7,8]. Additionally, larger tumors require a higher radiation dose [6,7,9]. For example, uveal melanoma is a radioresistant tumor, often requiring a prescription dose of up to 85 Gy to the apex of the lesion. While this dose is already likely to result in radiation retinopathy, thicker lesions result in significantly higher doses to the sclera, surrounding retina, and other vital ocular structures. While a multidecade systemic analysis by Kinaci-Tas *et al.* [2] reported radiation retinopathy in patients receiving more than 50 Gy of radiation, some studies have reported the development of radiation side effects to the retina after as little as 15 Gy [10]. Kinaci-Tas *et al.* [2] note that a threshold of 50 Gy likely underestimates the incidence of retinopathy because patients who received less than 50 Gy may not have received an ophthalmic examination unless they were symptomatic . A recent literature review spanning more than four decades by Shen *et al.* [11▪] described a predictive model that suggests that pediatric patients requiring 42 and 62 Gy have a relative risk of 5 and 50% of developing radiation retinopathy, respectively. However, there remains no universally accepted radiation threshold for the onset of radiation retinopathy.

Tumors closer to the optic disc and macula are at the highest risk of developing clinically significant radiation-related side effects and subsequent vision loss because of increased radiation exposure to those vital structures [12,13]. Finger found that radiation retinopathy development in patients with posterior tumors had an overall incidence of 52%, whereas in those with anterior tumors, it was as low as 4% [12]. Among other factors, this contributes to patients with tumors posterior to the equator having a worse visual prognosis compared to patients with lesions located anteriorly [12].

The type of radiation and dose fractionation used for treatment also influence the likelihood of

developing radiation-related side effects to the retina. It has been reported that gamma knife radiosurgery confers the highest risk of developing radiation retinopathy in patients with choroidal melanoma compared to brachytherapy, external beam radiotherapy, and proton beam radiotherapy, with about 50% of patients eventually developing severe vision loss [14,15]. Differences in retinopathy risk between radiation modalities are largely influenced by the treatment's ability to localize dosage to the primary malignancy. Plaque brachytherapy and proton beam radiotherapy provide targeted treatment that limits incidental radiation exposure of vital ocular structures, however there are limitations in the use of these modalities related to their availability as well as tumor size. External beam radiotherapy provides more broad exposure to the eye leading to increased incidental radiation to critical structures like the macula and optic disc; however, it is widely available and can be used to treat larger tumors as well. Therefore, while some treatment modalities may place the eye at an increased risk for radiation retinopathy, other clinical factors may influence a physician's treatment plan. Patients undergoing therapies that provide broad radiation with increased incidental exposure to the eye are at an increased risk of developing radiation-related side effects to the retina and may warrant closer monitoring [7,16].

While characteristics of radiation therapy and a patient's malignancy contribute to the risk of radiation-related side effects to the retina, so do patient comorbidities [3–5]. Diabetic retinopathy shares a similar pathogenesis to radiation retinopathy. Synergistic effects between radiation and diabetes have been reported to increase the risk of developing permanent vision loss by as much as 300-fold, so patients with comorbid diabetes should continue to closely monitor their blood glucose levels [4,17▪]. Encouraging multidisciplinary management to help patients maintain a healthy lifestyle (i.e. smoking cessation, diet, etc.) is an important aspect of care in limiting negative outcomes following radiation treatment.

PATHOPHYSIOLOGY

Radiation retinopathy can be divided into two stages: nonproliferative and proliferative (Fig. 1). The nonproliferative phase is characterized by endothelial cell damage and apoptosis due to free radical formation, caspase 3 activation, and cell cycle arrest [7,18,19]. Endothelial damage leads to increased vascular permeability, macular edema, and subsequent decreased vision. Damaged cells also trigger an inflammatory cascade resulting in increased

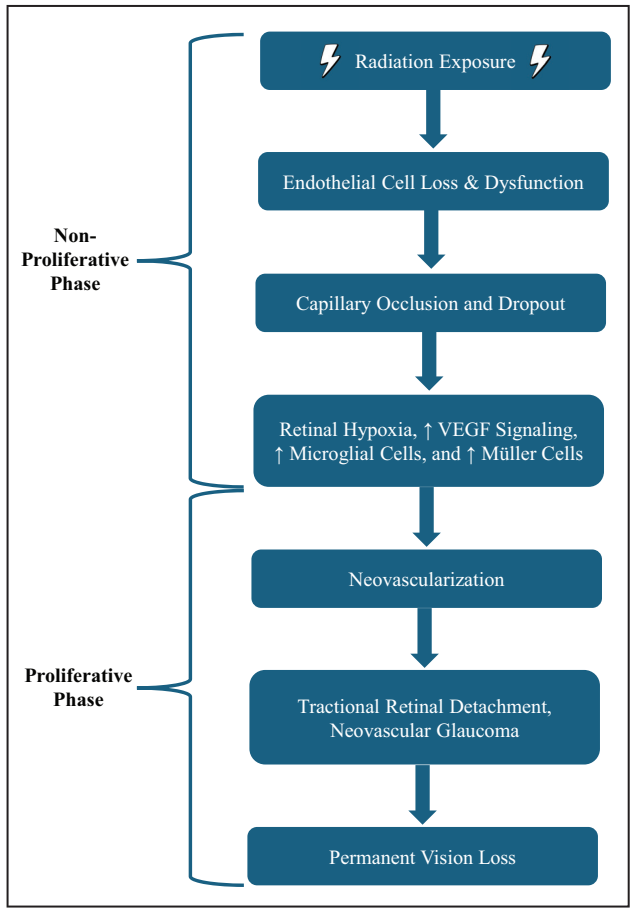

FIGURE 1. Pathogenesis of radiation retinopathy. Following radiation treatment, patients can experience a predictable pattern of endothelial cell dysfunction, ischemia, neovascularization, and permanent vision loss.

Müller cell activation, which may harm photoreceptor cells by disrupting the blood-retina barrier [8,20]. Additionally, while still not completely understood, upregulation of proinflammatory cytokines such as IL-1β, IL-6, TNFα, and TGFβ has been seen due to radiation damage [21]. These cytokines play a critical role in the development of ischemia due to further disruption of the blood-retina barrier. Endothelial damage and cytokine upregulation can also lead to downstream hypercoagulation effects due to leukocyte and platelet activation which subsequently cause microvascular occlusion and ischemia [7,8]. This results in the development of collateral vessels, microaneurysms, and dilated capillaries [7,18]. Microglial cell activation secondary to retinal injury following radiation also contributes to the upregulation of proinflammatory cytokines further contributing to radiation retinopathy [19,22]. Additionally, vascular endothelial growth factor (VEGF) has been shown to be elevated compared to controls not only in patients after radiation treatment, but even in patients with uveal melanoma prior to

treatment, potentially further increasing the risk of complications from radiation retinopathy [23]. As VEGF levels increase, worsened by retinal ischemia, neovascularization of the retina, iris, and iridocorneal angle can develop [7]. If untreated, neovascularization may cause vitreous hemorrhage, tractional retinal detachment, neovascular glaucoma, and potentially complete vision loss [7,18].

DIAGNOSTIC GUIDELINES FOR RADIATION RETINOPATHY

Despite a predictable pattern of disease, there is currently no universally accepted definition of radiation retinopathy. However, historically, most clinicians have utilized clinical examination in combination with diagnostic imaging to guide their diagnosis and decision-making. The fundoscopic examination may demonstrate microaneurysms, retinal hemorrhage, cotton wool spots, hard exudates, vitreous hemorrhage, vascular telangiectasias, neovascularization, sclerotic vessels, and macular edema (Fig. 2). Clinical findings are typically unilateral or asymmetric depending on the field of radiation, and the findings can vary greatly from patient to patient [24]. Since patients may be asymptomatic when they develop radiation retinopathy and disease can occur as early as one month or as late as 15 years following treatment, consistent clinical evaluation is critical [24,25].

Multimodal imaging has enhanced the diagnosis and management of radiation retinopathy. Fundus photography, in particular ultra-widefield photography, has allowed providers to better document changes over time, including in the far periphery [26]. Fluorescein angiography allows for visualization of capillary nonperfusion and neovascularization of the retina, which can be difficult or impossible to detect clinically [26]. However, advances in optical coherence tomography (OCT) and

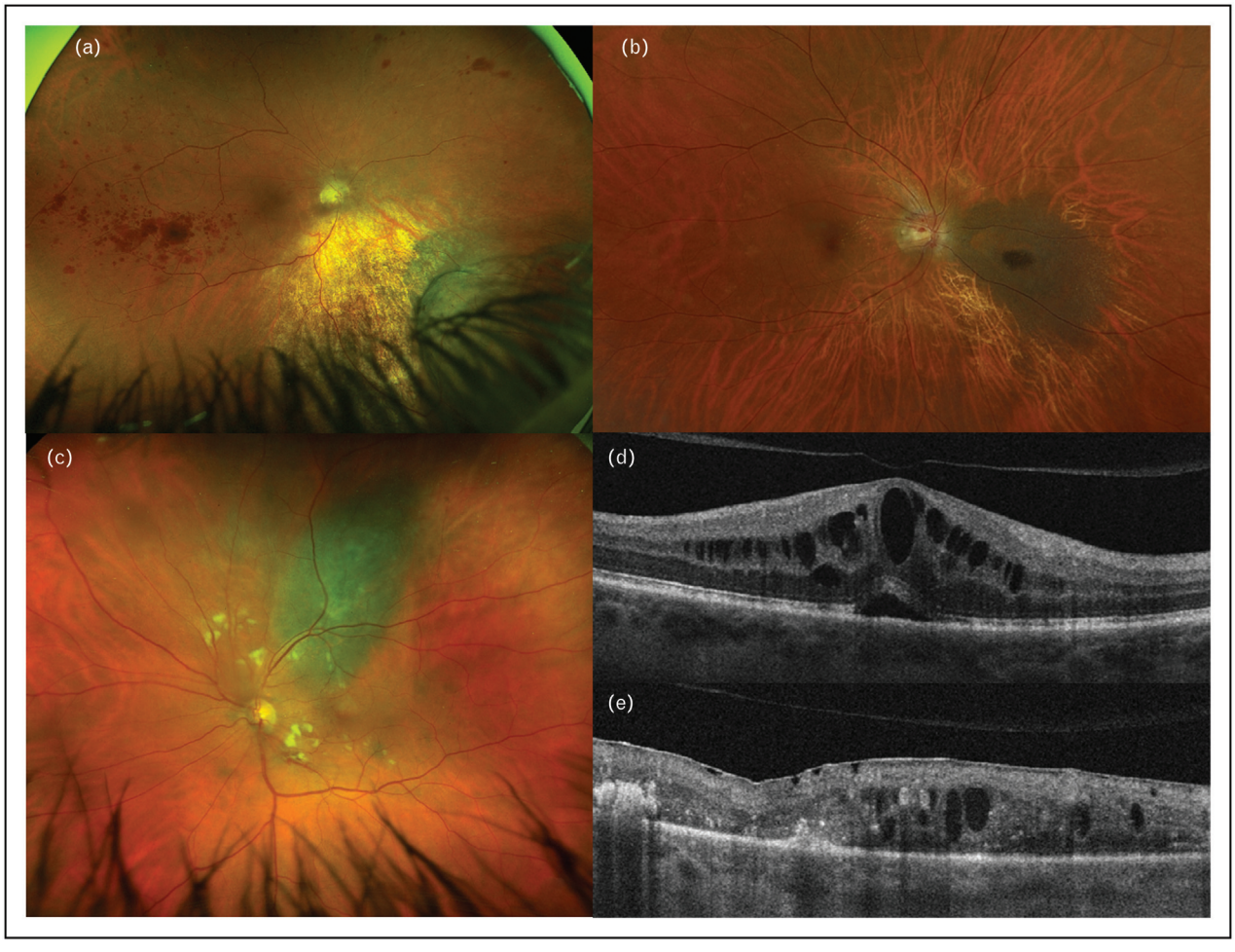

FIGURE 2. Common findings of radiation retinopathy. Ultra-widefield pseudocolor fundus photographs showing retinal hemorrhages and sclerotic vessels (a), radiation papillopathy with optic nerve edema, hemorrhages and hard exudates (b), and cotton wool spots (c). OCT showing early macular edema and subretinal fluid (d), and chronic macular edema with intraretinal deposits and loss of retinal laminations (e).

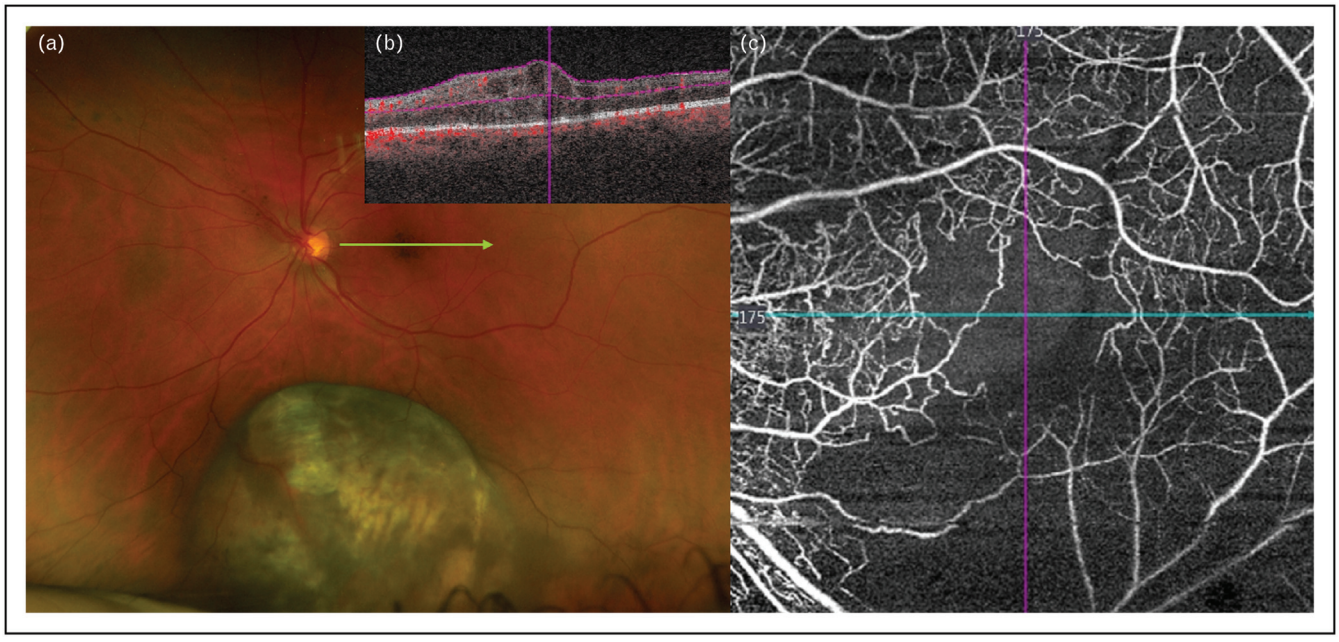

FIGURE 3. Findings on optical coherence tomography and OCT angiography following plaque brachytherapy. Ultra-widefield pseudocolor fundus photograph demonstrating a treated large melanoma inferiorly (a). Corresponding macular OCT shows intraretinal edema and loss of retinal laminations (b). OCTA shows severe capillary drop out at the level of the superficial capillary plexus (c).

OCT angiography (OCTA) have had the largest impact in diagnosing radiation retinopathy earlier and have provided insights into the pathogenesis of the disease and potential for visually recovery. Key clinical findings on OCT include retinal edema, subretinal fluid, and retinal thinning [26]. In addition to the changes seen on OCT b-scans, OCTA can identify capillary dropout, enlarged foveal avascular zone (FAZ), retinal ischemia, and neovascularization without the invasiveness of fluorescein angiography (Fig. 3) [27]. One study prospectively assessing peripapillary nerve fiber layer plexus capillary density, macular superficial vascular complex vessel density, and FAZ area showed no baseline differences between the eye with melanoma and the control fellow eye prior to treatment [28]. However, following radiation treatment, a 1% change in macular superficial vascular complex vessel density was associated with a high likelihood of developing radiation retinopathy at 24 months, indicating that monitoring these subtle subclinical changes may identify treatable disease before it can be detected clinically or even on OCT [28]. Interestingly, OCTA has also demonstrated choroidal ischemia in patients with uveal melanoma treated with radiation, indicating that radiation retinopathy may not be a comprehensive term for the damage caused by radiation and that visual impairment may develop, persist, and progress even with appropriate treatment of the retinal complications due to underlying choroidal changes [29,30].

Ultimately, unilateral clinical and imaging findings in a patient with a history of radiation exposure should raise suspicion for radiation retinopathy. Differential diagnosis should include hypertensive and diabetic retinopathy, retinal vascular occlusions, sickle cell retinopathy, Coats disease, ocular ischemic syndrome, and toxic tumor syndrome [17▪,24,31]. Patients with diabetes and hypertension may warrant closer monitoring following the completion of radiotherapy given the increased propensity for developing radiation-related side effects to the retina [24].

Although there is a lack of consensus, attempts have been made to create a grading system for radiation retinopathy. Classification systems have continued to evolve as improved diagnostic tools have led to more detailed criteria focusing on the level of neovascularization, elements of the fundoscopic examination, and the presence of macular edema [7,27,32,33]. In 2005, Finger and Kurli [34] proposed a classification system focusing on fundoscopic and angiographic changes associated with radiation retinopathy. In this classification system, stage 1 is defined by the presence of extramacular ischemic changes in less than five disc areas, microaneurysms, cotton wool spots, and exudates, stage 2 by macular ischemic changes, stage 3 by macular

ischemic changes with retinal neovascularization, and stage 4 by stage 3 findings with vitreous hemorrhage or five or more disc areas of retinal ischemia on angiography [34]. In 2008, Horgan *et al.* [26] focused on using OCT to describe macular changes following radiation. Grade 1 of radiation maculopathy exhibited extra-foveolar noncystoid edema, grade 2 extra-foveolar cystoid edema, grade 3 foveolar noncystoid edema, grade 4 mild to moderate foveolar cystoid edema, and grade 5 severe foveolar cystoid edema [26]. Incorporating aspects of the original classification systems by Finger and Kurl and Horgan *et al.* [26,34], Veverka *et al.* [27] proposed a new classification system in 2015 that focused on the earliest detectable changes currently known using OCTA. According to this system, radiation retinopathy is graded on a scale ranging from 0 (no clinical manifestations of radiation retinopathy) to 5 (OCTA unreadable due to extensive macular edema) [27]. Grade 1 is characterized by the presence of findings on OCTA exclusively, such as microaneurysm, discontinuity of retinal vasculature and widened FAZ, grade 2 by the presence of increased central macular thickness, grade 3 by cystoid macular edema visible on OCT, and grade 4 by clinically detectable signs of radiation retinopathy on fundoscopic exam [27]. However, radiation retinopathy classification systems are rarely used in clinical practice largely because they do not impact treatment considerations.

PREVENTION OF RADIATION RETINOPATHY

The Collaborative Ocular Melanoma Study reported that nearly half (43%) of patients treated with plaque brachytherapy developed vision of 20/200 or worse within three years of treatment [1,35]. The primary method to prevent the development of radiation retinopathy is to limit the amount of radiation exposure. This can be achieved through targeting therapies for head and neck cancers and reducing radiation doses, but caution is advised against reducing radiation dosage to the point that malignancies are undertreated [17▪,35]. In recent decades, the development of more targeted radiation modalities such as plaque brachytherapy and proton beam radiotherapy has successfully limited broad irradiation.

When it comes to utilizing teletherapy for the treatment of intraocular malignancies, proton beam radiotherapy offers a better side effect profile compared to gamma knife radiosurgery and external beam radiotherapy, as protons deliver most of their energy once they hit the tumor target, with minimal radiation affecting surrounding healthy ocular structures [36]. Unfortunately, not all malignancies are suitable for proton beam radiotherapy and this treatment modality is not widely available in the United States and worldwide due to cost-related restrictions [36]. In instances where stereotactic radiosurgery or external beam radiotherapy are necessary for either intraocular or head and neck tumors, hyperfractionation or intensity-modulated radiation therapy (IMRT) can decrease the risk of retinopathy [37]. Hyperfractionation divides the amount of radiation delivered to a patient over time, achieving the same total dose but allowing the retina to recover between sessions [37]. IMRT is a technique that utilizes concave radiation dose distributions to focus treatment more precisely on the tumor and away from surrounding structures [38]. This allows for more targeted radiation, limiting broad exposure, and potentially sparing surrounding healthy ocular structures from significant doses of radiation, thus lowering the risk of radiation retinopathy [37,39].

Advancements in plaque brachytherapy have also been beneficial. Plaque customization, including asymmetric loading of the radioactive seeds and plaque shape modification, offers the potential to greater concentrate tumor radiation while limiting exposure to adjacent structures [40,41]. Additionally, some centers are exploring the use of radiation dose reduction with early results suggesting equal efficacy to the standard dose of 85 Gy to the tumor apex [42]. However, additional studies are required to determine if these techniques are more effective at lowering incidental exposure to surrounding structures without increasing the risk of local recurrence, metastasis, and overall mortality [40]. It is important to note that ultimately the treatment modality of choice for radiation treatment largely depends on local availability, tumor characteristics, and cost-related considerations, and successful treatment should always take priority over the side effect profile.

Additional considerations to reduce the risk of radiation retinopathy include both intraoperative techniques and postoperative prophylactic procedures. In-vitro testing suggests that silicone oil attenuates the effects of radiation to surrounding tissues, which has prompted some centers to routinely perform pars plana vitrectomy and temporary silicone oil placement at the time of plaque brachytherapy to try and reduce the side effects of radiation [43,44]. *In vivo*, patients showed lower central macular thickness on OCT compared to controls who did not undergo silicone oil placement [45], but the complexity of the surgery and risk of complications have limited widespread use of this technique. Another surgical technique others have considered

to reduce the risk of radiation retinopathy is surgical endoresection of intraocular tumors either before or after radiation. In one study evaluating patients with uveal melanoma treated with proton beam radiation followed by endoresection compared to historical controls, endoresection reduced the risk of neovascular glaucoma and secondary enucleation in selected patients, but there was no significant difference in visual outcomes [46]. Considering the risk of surgical complications, iatrogenic tumor spread, and mortality from air embolism, this procedure is not routinely performed.

Prophylactic procedures like laser photocoagulation and corticosteroid and anti-VEGF treatments either at the time of plaque removal or shortly afterwards have become a more common practice with multiple studies outlining their potential benefits [34,47–53]. Finger and Kurli [34] and subsequently Materin *et al.* [48] demonstrated that prophylactic sectoral laser photocoagulation targeting the retina surrounding the treated tumor can prevent or delay the development of radiation retinopathy and macular edema . This can be performed at the time of radiation administration or can be delayed if localized exudative retinal detachment precludes good laser uptake. Alternatively, this could be performed with fluorescein angiography guidance, targeting the areas of ischemic retina. Subtenon triamcinolone has also been demonstrated to reduce the risk of radiation retinopathy by Horgan *et al.* [52] and may be performed at the time of radiation treatment. Anti-VEGF injections have been shown to decrease the risk of radiation retinopathy and potentially improve overall visual acuity [49,51,53]. However, the treatment regimen varies greatly among these studies ranging from injections administered every 4–6 weeks to every 4 months, with no current consensus on the most effective regimen [49,51,53]. Additionally, a 2023 meta-analysis by Victor *et al.* [54▪▪] examining 2109 patients showed that prophylactic anti-VEGF bevacizumab can decrease the likelihood of developing radiation retinopathy and provides a 50% reduced risk of developing vision worse than 20/200.

Major limitations of the above-mentioned studies include either their retrospective nature or relatively small sample size. To examine the potential risks and benefits of intravitreal anti-VEGF, corticosteroids, and observation for radiation retinopathy, the Diabetic Retinopathy Clinical Research Network (DRCR) Protocol AL is currently enrolling patients and preparing to analyze the long-term effects of treating patients prophylactically with intravitreal faricimab or the 0.19 mg fluocinolone acetonide implant compared to observation [55]. This study will elucidate if prophylactic treatment of radiation retinopathy is beneficial when assessed prospectively, and potentially lead to approval from the Food and Drug Administration (FDA) for these agents to be used for patients with radiation retinopathy.

TREATMENT OF RADIATION RETINOPATHY

Following successful radiation therapy with appropriate tumor control, monitoring for radiation retinopathy must begin immediately. There remains minimal consensus on standard treatment protocols for patients with radiation retinopathy. To date, multiple treatment modalities including intravitreal anti-VEGF injections have shown efficacy, but none have received an FDA indication for radiation retinopathy [24]. However, because radiation retinopathy and diabetic retinopathy share a similar pathogenesis, treatments with FDA-approved medications for diabetic retinopathy such as bevacizumab, ranibizumab, aflibercept, and faricimab have commonly been used for radiation retinopathy [7]. A recent meta-analysis by Zhuang *et al.* [56▪▪] examining 922 patients with radiation retinopathy demonstrated that anti-VEGF treatment has led to improved best-corrected visual acuity compared to control groups, further strengthening the evidence of the benefits of their use. However, the effects of anti-VEGF injections are temporary so providers must develop appropriate treatment plans that balance injection frequency with the medication's effectiveness. Murray *et al.* [57] found that anti-VEGF injections at fixed intervals every 6 weeks provide significantly improved overall visual acuity, even though some patients may require more frequent injections. Finger *et al.* [58] noted that many patients require decreased time intervals between injections and increased medication doses the longer they receive anti-VEGF treatment. Additionally, patients often require anti-VEGF therapies in perpetuity [58]. The significant commitment required by patients in combination with the notable cost of many of these therapies, compels providers to carefully consider the benefits of treatment and treatment discontinuation if the visual prognosis is poor.

Similar to the treatment of diabetic retinopathy, intravitreal corticosteroids such as dexamethasone, triamcinolone, and fluocinolone can reduce the inflammatory effects of radiation by decreasing cytokines and helping to repair and restore the blood-retina barrier [59–63]. Currently, there are few studies with large sample sizes exploring corticosteroid use in patients with radiation retinopathy and even fewer have compared them to anti-VEGF therapies [59,62,64]. In patients with refractory

macular edema, switching from anti-VEGF to corticosteroid injections or vice versa has been shown to improve response [62,65]. To date, no studies have explored concomitant treatment with anti-VEGF and corticosteroid injections in patients not responding to their current treatment regimen [56▪▪]. While anti-VEGF medications are routinely used as first-line, given the risks of steroid-induced glaucoma and cataract development, steroids are a reasonable consideration for refractory disease [7,61,66].

Targeted laser photocoagulation has been used to limit the neovascular drive in patients with radiation retinopathy [34]. In the previously mentioned study regarding the use of targeted laser to prevent radiation retinopathy and maculopathy, Finger and Kurli [34] reported that brachytherapy results in an ischemic zone surrounding the plaque, which can be treated with laser photocoagulation. Additional laser targeted to other areas of retinal ischemia can be used to further decrease VEGF signaling and diminish the neovascular drive, which might theoretically prevent further vision loss secondary to proliferative radiation retinopathy. However, other studies focusing on diabetic retinopathy and retinal vascular occlusion have demonstrated that photocoagulation of ischemic retina does not lead to a significant reduction in the need for anti-VEGF injections, and laser photocoagulation can lead to permanent visual field defects [67,68]. Despite the potential side effects, targeted laser photocoagulation is still used in select circumstances [47,56▪▪,59].

Progressive and uncontrolled radiation retinopathy can eventually require surgical intervention as progressively worsening neovascularization can cause vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma, which often results in permanent vision loss, severe pain, and potential loss of the eye. To preserve vision, vitrectomy for vitreous hemorrhage clearance and/or retinal detachment repair and photocoagulation may be considered. For neovascular glaucoma advanced glaucoma procedures like tube shunts, if deemed well tolerated enough to not risk extraocular extension of the tumor, or cyclophotocoagulation may be required [69]. However, some cases do ultimately result in secondary enucleation.

Recent efforts on potential future therapeutic targets for ischemic and proliferative retinopathies have focused on developing a better understanding of the inflammatory cascade, which is believed to be largely driven by Müller and microglial cell overactivation [8,19,70]. Further research is needed to understand the relevance of these elements in radiation retinopathy and if their targeting with novel therapeutic agents would effectively improve visual outcomes.

CONCLUSION

The prevalence of radiation retinopathy has increased since the adoption and more widespread use of eye-sparing radiation therapies for ocular malignancies. Using minimum effective doses of radiation, managing systemic comorbidities, and understanding the role of prophylactic treatment options are key to limiting ocular morbidity. Early detection of macular edema, ischemia, and neovascularization through new and noninvasive imaging modalities such as OCTA allows for early intervention. This highlights the value of maintaining a high index of suspicion to identify and carefully monitor at-risk patients with multimodal imaging.

The availability of intravitreal treatments such as anti-VEGF and corticosteroids has enabled providers to limit the sequelae of radiation-related side effects to the retina. The relative rarity of radiation retinopathy has so far precluded the feasibility of large prospective clinical trials focusing specifically on the prevention and treatment of this condition, resulting in radiation retinopathy not being included on the label for intravitreal anti-VEGF and corticosteroid medications. Hopefully, the DRCR Protocol AL clinical trial will open the door for physicians and patients to have access to the full range of prophylaxis and treatment options moving forward. Additional research in these areas will allow providers to more accurately counsel their patients, manage expectations, and improve disease control, potentially leading to better overall visual outcomes following radiation therapy.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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