REVIEW

Radiation-Induced Optic Neuropathy

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ABSTRACT

Radiation-induced optic neuropathy (RION) is a disabling late complication of radiotherapy leading to irreversible severe visual impairment or even total visual loss which may affect one or both eyes. Although not fully understood yet, RION is proposed to be a consequence of endothelial and neural cell injury with resultant necrosis. Risk factors include the patient and disease related factors, radiotherapy technique, per fraction and total radiotherapy doses. Currently there is no well-established treatment modality for RION, and usually the various drug therapies fail to reverse the visual loss. Therefore, currently the simplest but most effective treatment of RION is prevention of its occurrence by utilizing more sophisticated radiotherapy techniques and strict adherence to the published dose constraints for optic apparatus. Present review mainly aims to provide an overview of the currently accessible evidence on pathogenesis, risk factors, and treatment of RION.

Key words: Optic nerves, optic chiasm, risk factors, radiation-induced optic neuropathy, treatment.

Radyasyonla İndüklenen Optic Nöropati

ÖZET

Radyasyon optik nöropatisi (RON) radyoterapinin geç dönemde ortaya çıkan ve geri dönüşümsüz olarak bir veya iki gözü etkileyerek kısmi veya tam körlükle sonuçlanabilen şiddetli ve sakatlayıcı bir yan etkisidir. Her ne kadar altta yatan mekanizma henüz tam anlaşılabilmiş olmasa da RON'un endotel ve nöron hasarı ve bunlara bağlı gelişen doku nekrozunun bir sonucu olarak ortaya çıktığı öne sürülmektedir. RON risk faktörleri hasta ve hastalığa, radyoterapi tekniğine, radyasyonun toplam ve fraksiyon başı dozlarına bağlı faktörleri içerir. Güncel olarak RON tedavisinde kanıtlanmış etkin bir tedavi yöntemi bulunmamakta olup kullanılan ilaç tedavileri genellikle görme kaybını geri çevirmede başarısız kalmaktadır. Dolayısıyla RON'un güncel en basit ama aynı zamanda en etkili yöntemi gelişmiş radyoterapi tekniklerini kullanmak ve kılavuzlarda optik sinir ve kiazma için önerilen doz sınırlamalarına dikkat ederek gelişimini önlemektir. Bu derleme makalesinin temel amacı RON'un patogenezi, ilgili risk faktörleri ve tedavi yöntemlerini güncel veriler ışığında özetlemektir.

Anahtar kelimeler: Optik sinirler, optik kiazma, risk faktörleri, radyasyon optik nöropatisi, tedavi.

INTRODUCTION

Radiation therapy (RT) is an indispensable part of the primary management of tumors originating from nasopharynx, paranasal sinuses, skull-base, brain stem, midline intracranial structures such as hypophyseal and pineal glands, cerebellum and cerebral hemispheres. For such tumors, depending on the site and disease stage, RT can be utilized either as a single definitive treatment modality, or concurrent with or after chemotherapy, or adjuvant to surgery. Dose and fractionation schemes vary according to the primary tumor histology, tumor localization, disease stage, intent of treatment, and proximity of the index tumor relative to the critical structures. Irrespective of the RT technique, the main goal of RT is to deliver the maximum intended dose to the target volumes while keeping the organ at risk (OAR) doses as low as possible. In a typical head and neck or intracranial RT hypocampi, brainstem, pituitary gland, cochlea, bilateral parotid glands, optic chiasm, optic nerves, retina, and lenses constitute the most commonly considered OARs, with each having its own critical dose limits. Hence, keeping in mind the possibility of severe acute and more frequently late and potentially irreversible RT-induced severe toxicities, maximum effort should be spent to decrease the OAR doses at least below the defined tolerance limits.

In recent decades, the RT techniques had been significantly improved which resulted in safer ever delivery of higher doses to the target volumes and better sparing of the OARs. Nevertheless,

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despite of these innovations, it may be quite difficult to keep the OAR doses under the recommended tolerance limits in some certain tumors because of the high doses needed to achieve acceptable tumor control rates. Furthermore, currently not every center throughout the world has the access for these sophisticated RT techniques. Radiation-induced optic neuropathy (RION) is one such relatively rare but severely disabling late complication of external beam RT (EBRT) of head and neck, skull-base, or central nervous system tumors that usually causes uni- or bilateral irreversible vision loss within months to years of RT (1,2).

This review mainly aims to provide an overview of the currently accessible data on pathogenesis, risk factors, and treatment of RION.

PATHOGENESIS

Principally RION is widely considered as a delayed white matter disease characterized by tissue necrosis, however, to date related pathophysiological mechanisms have not been fully elucidated yet (3,4). RT induced microangiopathy, endothelial cell loss and demyelination are the main proposed contenders of RION pathogenesis (4). The tissue injury including the late necrosis is thought to be related with the radiation generated free radicals (1). Although the free radicals are normally involved in physiological functions such as cell proliferation and differentiation, and inflammation, excess production of free radicals may lead to pathological stress in tissues with deficient antioxidant defense mechanisms. Furthermore, fibrogenesis may be induced when the damage level rises up to levels where oxidative stress response transiently overwhelmed. Additionally, repeated or chronic stress may result in abnormal radical concentrations that may further intensify the fibrotic process by enhancing the production of reactive oxygen species (5).

The primary site of cellular damage is controversial, but probably the RION development process involves both the depletion of neuroglial progenitor cells and the vascular endothelium in a time dependent manner (6-8). Supporting this statement, Kline et al showed that the pathologic specimens of optic nerves with RION were exhibiting the all characteristics of typical ischemic demyelination, reactive astrocytosis, endothelial hyperplasia, obliterative endarteritis, and fibrinoid necrosis in a simultaneous manner (9).

Clinical Presentation and Diagnosis

Clinically, RION typically presents with acute, painless, and rapidly progressive monocular vision impairment or sudden total loss of vision. Although the general initial presentation may be restricted to one eye, but the other eye may also be affected during upcoming weeks to months. Usually the symptoms become evident around 6 to 24 months after RT. The peak for RION incidence is 1-1.5 years and vast majority of cases are diagnosed within 3 years of post-RT period (10). Central visual acuity is severely reduced in most affected cases, and presence of peripheral field defects consisting central scotomas, nerve fiber bundle defects, junctional scotomas, or bitemporal hemianopias are strongly suggestive for chiasmal or optic nerve injury. Although edematous optic disc may be apparent on ophtalmoscopic examination of anterior RION cases, this finding is usually absent in posterior RION if both compartments are not affected simultaneously.

As many benign conditions or tumor progression may mimic RION, and furthermore the lag time between the RT and symptoms may lead its diagnosis overlooked. Therefore, the diagnosis of RION can be made only if suspected in patients with previous history of head and neck or cranial RT after exclusion of all other causes. Considering the fact that the RION is an iatrogenic long-term complication of RT, the interval between the previous RT and onset of symptoms is of paramount importance for accurate diagnosis.

Imaging is quite important for RION diagnosis but the computerized tomography (CT) scans are usually reported to be within normal limits likewise the unenhanced T1 and T2-weighted MRI scans. Therefore, T1-weighted contrast enhanced MRI is the current gold standard imaging modality for RION which yields a marked segmental gadolinium enhancement along the optic nerve (4). Despite the contrast enhancement of the affected nerve or chiasm are widely accepted as the main radiological findings, yet, it is not pathognomonic for RION as optic neuropathies of other causes, optic neuritis, optic gliomas and other infiltrative lesions such as granulomatous involvement need to be excluded for an accurate diagnosis. However, contrast-enhanced MRI is usually recognized to be sufficient for RION diagnosis in the presence of appropriate history and physical examination (2, 3). Electrophysiological tests such as visual evoked potential (VEP) can also be helpful in earlier diagnosis of RION months before the settlement of visual symptoms.

Radiation Tolerance of Optic Structures

In 1991, Emami et al first defined the dose tolerance limits for optic apparatus with daily EBRT doses in the range of conventional fractionation (11). Accordingly, the authors defined 50 Gy and 65 Gy as the total EBRT doses for either of the chiasm and optic nerves to cause 5% and 50% toxicity risk at 5 years, respectively. However, the Emami and colleagues data was mirroring the

outcomes in a group of retrospectively assessed patients and their estimates were valid just for whole organ irradiation practices, which may be extremely conservative for partial-organ irradiation settings. The more recent Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) unlike the Emami data estimates the risk of toxicity for chiasm or optic nerve maximum point dose (Dmax) rather than the whole organ doses (12). According to QUANTEC doses for 3%, 3%-7%, and >7%-20% toxicity risks were estimated at 55 Gy, 55-60 Gy, and >60 Gy for optic nerves and chiasm. As the total dose of RT received by the optic apparatus appears to be the main determinant of RION development, dose as a risk and preventive measure will further be discussed in depth later in this manuscript.

RISK FACTORS

Factors which may predispose or aggravate the RION development incorporate patient and disease characteristics and the RT planning and delivery technique and dosing schedule; namely the treatment related risk factors.

Patient and disease characteristics

Patient- and disease-related risk factors may sometimes be as important as the treatment-related factors, because some particular patients groups might have considerably higher inherent RION risk after RT even though the dose tolerance limits have been met by the RT plan parameters. Such patients are considered to be more radiosensitive compared to general population; including those with increased age, comorbid diseases such as diabetes mellitus, vasculopaties, hypertension, collagen vascular disease, hormonal disorders, radiation hypersensitivity syndromes, continuing smoking habit, and chemotherapy delivered concurrently with RT (10,13). Hormonal therapy has been suggested to increase radiosensitivity in patients with growth hormone secreting pituitary tumors. Despite of the fact that concurrent chemotherapy is usually considered to be a strong risk factor for RION development, some chemotherapeutic agents may themselves be associated with RION in absence of RT. Vincristine, nitrosureas, taxanes, methotrexate, cisplatin, cyclosporine, and cisplatin are some examples for such agents known to induce or aggravate late neural toxicity (5,14).

External tumoral compression of the optic apparatus is a common feature of pituitary and nerve sheath tumors, midline gliomas, and metastatic tumors that is also suggested to induce RION, probably due to compression related ischemia (15). Recurrent infiltrative tumors may also present with symptoms mimicking RION, hence exclusion of tumor recurrences is imperative for an accurate RION diagnosis.

Treatment related risk factors

Then RION risk is also associated with the RT delivery method, total dose and fractionation parameters. Implementation of IMRT to routine RT practice enabled the radiation oncologists to deliver higher doses to the target volumes more safely and precisely either as a single fraction ablative dose or multiple fractions with lower per fraction doses. The main goal of fractionated RT is provision of enough time intervals to neighboring healthy tissues to repair the sublethal damage, and therefore, to increase their tolerance to higher tumoricidal doses. Considering the fractionated RT, the IMRT appears to be more advantageous than the other three-dimensional conformal RT techniques for reduction of the RION risk.

Risk of RION is considered to be minimal when Dmax of the optic nerve and chiasm doses kept below 54-55 Gy for ≤2 Gy per fraction doses. In this respect, because the risk of RION is minimal with a Dmax <55 Gy (particularly for per fraction doses ≤2 Gy fraction) the initial Emami estimate of 5% total visual loss at 5 years of treatment with a dose of 50 Gy Gy to the whole organ appears to be very low (11). Therefore, the QUANTEC doses for 3%, 3%-7%, and >7%-20% toxicity risks which were estimated at 55 Gy, 55-60 Gy, and >60 Gy for optic nerves and chiasm seems to be more accurate (12). Of importance, one exception for QUANTEC's range is the pituitary tumors where RION may develop at lower doses: even after 45-50 Gy administered in 1.67-2 Gy per fraction doses (16).

Per fraction dose size directly impacts the incidence of optic neuropathy. Although the data for RION incidence with hypofractionated RT (> 2 Gy per fraction doses) is limited, yet available evidence exhibited that larger per fraction doses were associated with significantly higher RION rates. For example, Harris et al (15) reported that the RION was more common with >2.5 Gy than the <2.5 Gy per fraction doses (18% versus 0%) in 55 patients with pituitary adenoma or craniopharygioma who received 45-55 Gy RT.

Stereotactic radiosurgery (SRS) is widely used in cranial tumors where ablative RT doses delivered usually in a single session (1 to 5 fractions by definition). In general, a single dose of 8-10 Gy is considered to be safe (17-19), while Pollock et al (20) reported that 12 Gy Dmax was safe with a low risk of RION in patients with no previous history of RT to the optic apparatus. In the recent excellent work by Hiniker et al (21), validating the optic pathway constraints of the

Dmax limits of 12 Gy in 1 fraction from QUANTEC (12), 19.5 Gy in 3 fractions from Timmerman 2008 (22), and 25 Gy in 5 fractions from The American Association of Physicists in Medicine (AAPM)Task Group 101 (23), all suggesting <1% RION risk, demonstrated that the all three suggestions were exactly valid considering the same constraints emerged in their probit dose-response model study consisting analyzable 262 patients.

TREATMENT

Currently there is no established treatment for RION and the agents researched were usually found to fail to achieve satisfactory reversal of the useful vision. The easiest but most effective maneuver is the prevention of RION by respecting the recommended radiation dose limits and identifying those patients groups with particular comorbidities which may decrease the tolerance limits of the optic apparatus below the specified limits (24). Therefore, as a thumb rule, the total and per fraction RT doses and the volume of optic apparatus residing in or nearby of the treatment volume should be kept at minimum as far as reasonably achievable without any sacrifice of the tumor control rates. Additionally, extreme care should be given for RT planning of patients with predisposing vasculopathies, neuropathies, collagene vascular diseases, diabetes mellitus, hypertension, and radiation hypersensitivity syndromes such as ataxia telangiectasia.

Investigations regarding the RION treatment mainly focused on the efforts to treat or alleviate the suggested primary mechanisms of radiation injury, namely the potentially reversible early inflammation and late hypoxic obliterative vasculopathy and associated necrosis. For this purpose, the most commonly used medications include the corticosteroids, systemic anticoagulants, angiotensin converting enzyme (ACE) inhibitors, intraocular triamcinolone acetonide, systemic or intraocular bevacizumab, and hyperbaric oxygen (HBO) therapy (Table 1).

Option	Recommended treatment
Corticosteroids	• 4-10 mg of i.v/oral dexamethasone is administered four times per day and decreased with a slow taper by 2-4 mg every 5 to 7 days • Alternatively, high dose (1 g/day) i.v methylprednisolone for 5 consecutive days, than switch to oral methylprednisolone (80 mg/day) for 7 days and slowly taper the dose on following several weeks
Systemic anticoagulants	Full anticoagulation with daily i.v heparin followed by oral warfarin for 1 week to 6 months.
ACE inhibitors	Starting 2 weeks after RT 1.5 mg/kg daily oral ramipril may be administered for 6 months to prevent RION development
Intraocular triamcinolone acetonide	Deliver 4 mg of triamcinolone acetonide (0.1 mL) into the vitreous through the pars plana with a 30-gauge needle using sterile technique when RION is diagnosis is settled
Bevacizumab	
Systemic	• 4 cycles of 7.5mg/kg of i.v bevacizumab every 3 weeks for 12 weeks
Intraocular	• Deliver 1.25 mg of bevacizumab in 0.05 mL into the vitreous through the pars plana with a 30-gauge needle using sterile technique, and repeat the injections every 6 to 8 weeks after a minimum of 2 initial injections
HBO therapy	Administer HBO therapy at 2.0-2.4 atmospheres partial pressure of oxygen chambers. Ideally initiate the procedure within 72 hours after symptom onset and continue for 20-30 sessions over the course of 30 days, with each treatment duration of approximately 90-120 min

Table 1. Treatment options for radiation-induced optic neuropathy.
Abbreviations: i.v: intravenous; ACE: Angiotensin converting enzymes; RT: Radiotherapy; RION: Radiation-induced optic neuropathy; HBO: Hyperbaric oxygen

Likewise, the other parts of the central or peripheral nervous system, the corticosteroids have been widely utilized for treatment of RION, but unlike the other sites the results are usually reported to be disappointing with only temporary improvements (13). Theoretically, use of systemic corticosteroids in RION basis on their antioxidant actions against radiation-induced free-radical injury, universal anti-inflammatory and anti-edematous, and anti-demyelinating properties. Unfortunately, steroids are unlikely to provide benefit in severe cases of RION.

Heparin and warfarin are the two anticoagulants which are suggested to impede and reverse small-vessel endothelial injury, and therefore, mitigate radiation-induced neurotoxicity. Prior studies scarcely demonstrated that the corticosteroid unresponsive late radiation-induced cerebral necrosis might recover to some degree when anticoagulated with heparin and/or warfarin (25,26). But unfortunately, these limited benefits may not be observed in cases with RION as it has been documented to occur even in patients under anticoagulation therapy for cardiac disease. Therefore, the usefulness of anticoagulation medications for RION remains to be determined despite of the theoretical promotion of blood-flow to irradiated tissues in presence of such drugs.

Ramipril is an ACE inhibitor that is capable to cross the blood-brain barrier. Basically, ramipril may prevent RION by inhibiting the radiation-induced axonal damage via decreasing pro-inflammatory cytokine secretion (27). Using a well-characterized optic neuropathy model in the rat Kim et al. (27) investigated whether ramipril would ameliorate radiation-induced brain damage after single dose of 30 Gy. Ramipril was started 2 weeks after irradiation at a 1.5 mg/kg/day dosage scheme in this experimental study. Rats were assessed for optic nerve damage functionally at 6 months of irradiation using VEP measurements and histological examinations. The authors reported that the ramipril administration conferred significant modification of radiation injury. Rats receiving radiation alone exhibited three-fold lengthened mean peak latencies in the VEP, while evoked potentials that resembled those of untreated control rats were reported in 75% of rats receiving radiation followed by ramipril. Thusly, prophylactic use of ramipril may prove valuable in prevention of RION when initiated within 2 weeks of RT completion.

Triamcinolone acetonide is a corticosteroid that exerts the same actions on target tissues via the same mechanisms utilized by its systemic counterparts. However, triamcinolone acetonide may allow for more direct treatment on optic apparatus by intravitreal injection. Acute radiation-induced papillopathy was shown to respond rapidly to single dose intravitreal triamcinolone acetonide injection with resolution of optic disk hyperemia and edema and modest return of visual acuity in 9 patients with papillopathy secondary to plaque RT for choroidal melanomas (28). However, the durability of response remains unknown as the mean follow-up time was only 11 months. In a recent study, Seibel et al further reported that the intravitreal triamcinolone acetonide was as effective as bevacizumab in terms of reduced central foveal thickness and visual improvement (29).

The monoclonal antibody targeting vascular endothelial growth factor, bevacizumab, has been proposed to mitigate radiation necrosis by reducing edema associated with decreased capillary leakage after its systemic administration (30). Providing a Level 1 evidence, the randomized double-blind controlled trial by Levin et al (30) involved 14 patients who had undergone irradiation for head-and-neck carcinoma or intracranial tumors with radiographic or biopsy proof of central nervous system radiation necrosis. Patients were randomized to receive one of intravenous bevacizumab or saline at 3-week intervals (control group). The authors defined the response or progression according to MRI findings 3 weeks after the second treatment course and clinical signs and symptoms at the same time point. MRI scans demonstrated that although no patient receiving saline responded (0%), all bevacizumab-treated patients did so (100%) with decreaments in T2-weighted fluid-attenuated inversion recovery and T1-weighted gadolinium-enhanced volumes. Furthermore, endothelial transfer constant was also decreased in the experimental arm. However, it should be kept in mind that bevacizumab itself may potentiate vascular insufficiency and promote ischemia and lead to paradoxic occurrence of RION after its use (31).

In cases of anterior RION, optic disc edema and hemorrhage may further be mitigated by intravitreal injection of bevacizumab by direct reduction of the optic nerve vascular permeability. Encouragingly, Finger et al in a series of 14 patients who developed anterior RION following plaque RT for choroidal melanoma demonstrated that the optic disc hemorrhage and edema were reduced in all patients with visual acuity being stabilized or improved in 9 (64%) of 14 cases at nearly two years after the minimum of 2 intravitreal injections of every 6-8 weeks (32).

The classical HBO therapy consists of the delivery of near 100% oxygen of 2 to 3 atmospheres by utilizing a specific pressurized chamber. Treatment usually incorporates serial dives of variable duration ranging from 30 to 120 minutes. Radionecrosis is a hypoxic/anoxic condition in

which the oxygen levels are extremely low to support physiologic neo-angiogenesis. Therefore, for RION, artificially increased high oxygen concentration by HBO therapy is proposed to disrupt the ongoing ischemic necrosis by enhancing angiogenesis, fibroblastic activity, and collagen synthesis in irradiated tissues. In an early report, Borruat et al (33) reported that the visual function was improved in 2 of 4 patients with RION after HBO therapy consisting 30 dives of 90 minutes each at ≥2.4 atmospheres. The authors recommended commencement of HBO therapy within 3 days of vision loss. Similar results were also reported by Malik and Golnik (34) where earlier initiation of HBO therapy at 2.5 atmospheres was recorded to be more effective than late onset HBO therapy. The 2 patients in their study who experienced visual decline in the less affected eye began treatment 7 and 9 days after initial vision loss, while the 2 patients who had preserved vision were treated at 2 and 5 days after the onset of visual decline. All received more than 30 days of 100% oxygen at 2.5 atmospheres for at least 60 minutes/day. In a literature review performed by Levy and Miller in 2006, the authors concluded that HBO therapy outcomes were variable at best and recommended that it should be initiated soon after the onset of vision loss in select cases without optic nerve pallor (35). Therefore, available limited evidence suggests the early initiation of HBO in select cases of RION presenting with relatively favorable features may be beneficial.

CONCLUSIONS

Although the RION is a relatively rare event after EBRT, yet it leads to severe visual complications including the devastating total visual loss in one or both eyes when occurs. Further complicating the poor condition, there are unfortunately limited data on effective treatment of RION and the currently available options usually fail to reverse the already settled radiation injury. Therefore, in absence of clinical guidelines or consensus statements treatment of the RION, the current best treatment is its prevention by adhering the published dose tolerance limits for optic apparatus. Available data suggests that the early detection of RION and timely commencement of antiangiogenic bevacizumab, HBO, and ACE inhibitors may prove beneficial effects on prevention and treatment of RION in select patients groups.

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