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REVIEW

Radiation-Induced Optic Neuropathy: Literature Review

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ABSTRACT

Radiation-induced optic neuropathy (RION) is a rare disease caused by exposure of the optic nerves to radiation during radiotherapy procedures for head and neck tumours. The purpose of this study was to review and summarise the epidemiology, risk factors, clinical presentations, pathphysiology characteristics, diagnosis, and management of RION. Its occurrence is associated with cumulative doses of radiation above 50 Gy, presence of multi-morbidities and the presence of concomitant chemotherapy and radiotherapy. It manifests with acute, painless, and monocular loss of vision, and these symptoms appear late after the radiation exposure. The diagnosis of the disease occurs by exclusion and, mainly, by the clinical analysis of the case associated with the time of radiation exposure. Treatment does not seem promising and there is not an effective cure. In this review, we mainly focus on compiling existing information on the topic and providing knowledge for early diagnosis and more efficient treatment.

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Introduction

Radiotherapy (RT) is a therapeutic modality in which the systemic repercussion is limited because its performance is restricted to the field in which it is applied, although this modality of treatment is not free from the occurrence of complications, which may be late, acute, rapidly progressive and also irreversible.[1]

Complications resulting from RT are usually associated with total dose, fractional dose and whether or not it is associated with chemotherapy.[2] Besides, they are also divided into early (occurring during treatment duration and up to 1 month after treatment completion) and late (occurring months to years after completion of treatment).[2–4] Acute complications are usually associated with the bone marrow, gastrointestinal tract, and skin (and usually resolve within a short time). Delayed complications are associated with damage to the liver, kidneys, and central nervous system (CNS), and are often only partially reversible.[3]

Among the late complications of RT are radiation-induced optic neuropathy (RION), which results in expressive and irreversible loss of vision, due to cumulative dose of radiation—typically higher than 50 Gy.[5–7] RION typically presents with acute, painless and monocular vision loss, but the development in the second eye can occur simultaneously or sequentially.[5] According to Kline et al.,[8] Borruat et al.[9] and Danesh-Meyer,[7] this disease can occur within 3 months and up to 8 years after exposure to RT, and this latency period is inversely proportional to the radiation dose received by the patient.

Therefore, this work proposes to review the literature on RION, addressing epidemiological data, risk factors, pathophysiology, diagnosis, and treatment.

What is RION?

RION is classified as a type of ischaemic optic neuropathy, a classification that includes other types of optic neuropathies, such as, for example, non-arteritic, diabetic, and arteritic anterior/posterior. The term ischaemic is used to define these types presumably caused by ischaemia, as the name itself suggests.[10] RION occurs through delayed radionecrosis of the anterior visual pathway, with severe loss or reduction of visual acuity, which can be unilateral or bilateral, is often irreversible, and is caused by exposure to external cranial RT for the treatment of tumours of the brain, skull and sinus. It can arise from months to years after exposure.[10–13]

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RION history

Before writing about RION, it is important to report that although RT is an important tool for cancer treatment, its use can still be carcinogenic, as well as some chemotherapeutic drugs, and may be correlated with the appearance of secondary malignancies. In addition, these treatments can lead to the development of several adverse effects that impact the patient's quality of life.

Oncological malignancies have resulted from nuclear and/or radiological accidents, when individuals have been exposed to radioactive sources. Corroborating this, Ozasa et al.[14] wrote that exposures from the largest nuclear disasters in human history—first in Hiroshima and soon after in Nagasaki—provided clear evidence that ionising radiation is a human carcinogen. Significant increases in blood, breast, and other cancers were observed in atomic bomb survivors.[14]

It is generally accepted that children are more sensitive to radiation than adults, specifically with higher relative risk of cancers including leukaemia, brain, breast, skin, and thyroid cancers.[15] In part, this is because of the radiosensitivity of their developing organs and tissues but also due to their longer post-exposure life expectancy. This increases the lifetime risks of developing radiation-induced malignancies.[16–18] This is becoming important because 70% to 80% of all children diagnosed with cancer now have long-term survival.[19]

RION could be considered an adverse effect from RT used for treatment of head and neck malignancies. The first reported case of RION, which was not recognised as one of the complications of the use of radiation in medicine until the 1950s, correlated with the attempt to ablate the pituitary gland in patients with advanced breast cancer.[20] The report from Forrest et al.[21] is regarded as the first to describe the occurrence of this disease, describing it as a complication of brachytherapy. In 1957, another report of RION was published, this time caused by teletherapy.[20–22]

Epidemiology and risk factors of RION

RION is a rare complication of RT, and therefore this makes it difficult to create broad and general recommendations. It may however be one of the most common side effects of RT in the treatment of nasopharyngeal carcinoma.[7,23,24] The dose used in the treatment of patients with tumours of the head and neck is the main risk factor for the development of the disease. Consequently, the maximum safe dose of radiation to be received by the anterior visual pathway is established from the risk of developing RION.[12,15,25,26]

According to Seregard et al.[25] the damage to the optic nerve is related to the total dose, volume of optic nerve irradiated and fractionation. It has already been shown that the anterior visual pathway does not tolerate cumulative doses greater than 50 Gy and fractional doses greater than 2 Gy. In addition, it is reported that the increase in the incidence of RION is proportional to the increase of these doses.[2,23,26–30] However, more recent data indicate that a single dose less than 12 Gy will induce RION in 1% of patients.[31,32] Data also suggest that no patient receiving less than 8 Gy to the anterior optic pathways will develop RION, but the frequency rises steeply to 78% when the dose is 15 Gy or more following stereotactic radiosurgery, whose the security dose is less than 8–10 Gy.[6,25] Fractionation significantly reduces radiation toxicity and for doses at <1.8 Gy per fraction, radiation damage increases markedly first when the total dose is more than 60 Gy.[25] A similar increase in radiation toxicity is evident for single doses above 12 Gy.[33]

Table 1 shows the incidence of RION in some retrospective cohort studies that analysed the efficacy of treatment with external radiation (RT with teletherapy) in different types of tumours, verifying the occurrence of complications in the long term. Several studies, including those outlined in Table 1, corroborate the need for a safe dose of radiation in the treatment of head and neck tumours. Somani et al.[34] obtained an RION incidence of approximately 50% after an external radiation dose of 70 Gy in five fractions, while Kim et al.[35] reported an incidence of 0% with a prescribed mean dose of 50.4 Gy in 28 fractions.

Bhandare et al.[36] reported a lower risk of RION development with the use of hyperfractionated RT (more than one daily dose) compared with a conventional daily dose, showing greater safety with the use of this therapy in a retrospective cohort

Table 1. Retrospective cohort studies that analysed the efficacy of radiotherapy treatment and the occurrence of post-exposure complications (including RION) in head and neck tumours.

Author/Year	Study period	Location and type of tumour	Total number of patients in the study	Mean prescribed dose/fractions	Number of occurrences of RION	Study follow- up period
Wang et al., 2017[39]	2008–2014	Cavernous sinus haemangioma	31	21 to 22 Gy in 3 to 4 fractions	0	30 months
Astradsson et al., 2017[40]	1999–2015	Craniopharyngioma	60	54 Gy (1.8 or 2 Gy per fraction)	1	22 years
Astradsson et al., 2014[41]	1999–2009	Meningioma of base of skull	39	54 Gy (1.8 or 2 Gy per fraction)	4	2 years (minimum)
Astradsson et al., 2014[41]	1999–2009	Pituitary adenoma	55	54 Gy (1.8 or 2 Gy per fraction)	7	2 years (minimum)
Kim et al., 2013[42]	1998–2007	Pituitary adenoma	76	50.4 Gy (28 fractions)	0	Mean 6.8 years
Somani et al., 2009[43]	1998–2006	Choroidal melanoma	64	70 Gy (5 fractions)	33	26 months
Elhateer et al., 2008[44]	2000–2005	Pituitary macroadenoma	13	50.4 Gy (1.8 per fraction)	0	Mean 24 months
Selch et al., 2004[45]	1997–2002	Cavernous sinus meningioma	45	50.4 Gy (1.8 per fraction)	0	3 years

study involving 273 patients, who received RT for some tumours of the head and neck. Girkin et al.[37] performed a series of four reports of RION cases after stereotactic radiosurgery for the treatment of suprachiasmatic tumours, in which the patients received a single dose (ranging from 7 to 14 Gy), indicating the possibility of occurrence of the disease even at low dosages when applied in single doses.

Concomitant chemotherapy has already been pointed out as a potential risk factor for RION.[38] It is suggested that chemotherapeutics, such as vincristine, nitrosourea, and cisplatin, are associated with direct optic nerve toxicity and may have a radiosensitising action thus increasing the risk of RION development in patients receiving adjuvant chemotherapy.[39–41] Also, vascular disorders have also been associated with a higher risk or RION occurrence including hypertension, hyperlipidaemia, and smoking.[23,42] However, Ferguson et al.[23], in a case-control study involving 14 patients who developed RION compared with 31 controls who did not, and who both received the maximum radiation dose to the optic pathways, found no significant association between hyperlipidaemia, diabetes, advanced age, and hypertension. Bhandare et al.[36] also found no significant association between RION and hypertension and diabetes, but they point out, similarly to Ferguson et al.[23], that this may be related to the low incidence of the association between these diseases which makes it difficult to carry out systematic analysis that can prove the risk factors for RION.

Pathophysiology of RION

Despite constant efforts and studies to increase the safety of the use of RT, thus adopting the best treatment plan, there is unpredictability as to whether damage to healthy surrounding tissues will occur.[11] The bystander effect has been identified as a possible cause of this unforeseen event. It is a lesion of the cells adjacent to the cells affected by a minimal amount of alpha (α) or gamma (γ) particles, by the transmission of damage signals through communicating junctions.[43–46]

Nonetheless, it is reported that the pathophysiology of RION is not well understood, but the main theories point to an ischaemic component as the main factor, since it is a late complication of RT and associated mainly with a CNS white matter disorder.[7,23] It is also believed that this injury is triggered by the release of free radicals induced by RT, causing damage to normal tissue. However, the primary site of this damage is still unknown, but may be the vascular endothelium and neuroglial progenitor cells.[11,47–49] Since radiation causes damage mainly to the white matter, it would be expected that the main damage would be to this element. Studies have shown damage to the cerebral vascular endothelium of rats and also the human optic nerve.[50,51]

In addition to these factors, which can directly lead to loss of visual function, another item is also included to be involved in RION pathophysiology, namely somatic mutations in glial cells, producing metabolically inefficient cells and leading to demyelination and neuronal degeneration of endothelial cells.[7,52]

Regardless of the triggering component of RION, Lessel reported the outcome is related to the "3-H tissue" components: hypovascularity; hypocellularity; and hypoxia.[11] According to him, all of these processes contributed to neuronal degeneration and consequent severe loss of vision, with the final pathology of RION being characterised by stenosis and vascular occlusion, loss of the myelin sheath and axons and the presence of fibrinous exudate.[11,53,54]

A comparison could be made with the pathophysiology of radiation retinopathy, which is better understood, since this one is the most common complication of the posterior segment irradiation, but RION also occurs frequently. According to Seregard, radiation retinopathy is a chronic and progressive vasculopathy of the retinal capillaries primarily caused by endothelial injury to the vessel walls after RT, which causes capillary dilation, increased vascular permeability, endothelial sloughing, thrombosis, retinal cotton wool spots, retinal exudates and haemorrhages. Later, there is loss of pericytes as well as endothelial cells resulting in capillary drop-out and full-thickness retinal atrophy.[25] All this knowledge about radiation retinopathy could lead a better understanding of RION, but in radiation retinopathy only the postlaminar optic nerve is involved. The clinical appearance is subtle with just progressive pallor of the optic nerve head.[7,55,56] The pathogenesis is believed to include axonal necrosis or a combination of these.[7]

As therefore mentioned, the pathophysiology of RION is not yet well known, but is believed to be related primarily to white matter injury in association with vascular endothelial injury and damage to neuroglia progenitor cells (both destroying these cells and creating metabolically inefficient cells) that will lead to demyelination and subsequent neuronal degeneration.[7,11,47–49,52]

Clinical presentation of RION

RION typically presents with acute, intense, painless, irreversible, and monocular loss of vision (with the other eye variably being affected either simultaneously or at a later date). RION occurs after a latency period that may range from months to years after exposure to RT.[5,7,12,13,25] The incidence of RION is rare and depends on the nature of the irradiated tissue: 0.53% among partially resected adenomas; 2.04% among partially resected anterior visual pathway meningiomas; and 8.7 to 9.0% among tumours of the nasopharynx, nasal cavity, and paranasal sinuses.[31,36,57,58] In two cases reported by Archer et al.,[13] patients received radiation distributed across the entire brain, and both displayed prechiasmatic optic nerve enhancement, suggesting that this anatomical area may be relatively vulnerable to delayed radionecrosis, but there are no previous reports of whole brain radiation leading to RION.[7,11,13,38,58–63]

The occurrence of the disease significantly affects the patients' quality of life, whose visual acuity is less than 20/200 (about 85% of the cases), with most of the cases progressing to no light perception (45% of cases).[7,24,52,64]

Speckter et al.[12] reported that RION occurred in a period of 10 to 20 months (mean of 18 months) after treatment, while Danesh-Meyer[7] reported that visual loss occurred within 3 months to 9 years after exposure to RT. Most cases seem to develop within about 3 years after completion of RT treatment.[9] And, as previously mentioned, there is an inversely proportional relationship between this latency period and the radiation dose used in therapy.[9,36]

Other factors may be present and reported by patients in addition to the symptoms described above. Acute vision loss, which may worsen in days or weeks, may be preceded by the transient occurrence of mono- or binocular visual loss.[7,64] The visual field may show patterns of optic or chiasmatic defects including central scotoma, bitemporal hemianopia or a junctional syndrome with ipsilateral diffuse loss and contralateral temporal hemianopia.[7,9]

On ophthalmoscopy, because RION is more commonly a retrobulbar process, the optic nerve may be normal in the acute phase.[7] Only when the ischaemic process occurs anteriorly to the cribriform plate will there be oedema, but the pallor and atrophy of the nerve, due to the low vascularisation, occur independently of this fact and begins to develop in 6 to 8 weeks from the beginning of symptoms. So, RION can occur in two ways: anterior ischaemic optic neuropathy (when ischaemia affects the region

anterior to the cribriform plate) or retrobulbar ischaemic optic neuropathy, with both forms potentially also occurring simultaneously.[7,20]

Diagnosis of RION

The diagnosis is made by exclusion but should be suspected when the visual loss occurs after exposure to RT at an appropriate latency time. Danesh-Meyer pointed out as a diagnostic criterion the presence of evidence of optic neuropathy or irreversible chiasmatic dysfunction (visual loss or visual field deficiency) in the absence of other causes, making it a diagnosis of exclusion.[7]

The main hypothesis to be rejected when RION is suspected is the recurrence of the tumour for which the patient received RT.[7] The most important difference is often the slow progression of visual loss in tumour recurrence. Other less common differential diagnoses include radiation-induced neoplasms, arachnoid adhesions around the optic chiasm, and giant cell arteritis—this one being primarily considered in patients over 60 years of age.[7,8,20]

Imaging in RION diagnosis

RION may be associated with characteristic findings on neuroimaging.[7] On ophthalmoscopy there may be scattered vascularisation, "flame-shaped haemorrhage," optic nerve atrophy and "cotton wool spots".[65] Early stage fluorescein angiography may show retinal arterial narrowing, punctate and dispersed haemorrhages, and retinal microaneurysms. In the late phase, there may be no perfusion, telangiectasia, macular and disc oedema.[25,65] Also, optical coherence tomography may demonstrate macular oedema.[66] According to Danesh-Meyer,[7] electrophysiological testing has also been shown to detect early signs of radiation damage to the visual pathway.

Computed tomography and non-contrast magnetic resonance imaging (MRI) usually appear normal. Thus, the radiological appearance of the optic nerves in RION is non-specific and may be indistinguishable from that in idiopathic optic neuritis, sarcoid optic neuropathies, optic glioma, or another infiltrative optic neuropathy.[7] However, the T1-weighted MRI image with gadolinium contrast may show enhancement of the optic nerve and chiasm.[38,59] Zhao et al.,[65] in a descriptive retrospective study, besides reporting enhancement with gadolinium on MRI of the optic nerve, chiasm and optic tract, also observed tortuosity, border irregularity and atrophy of the optic nerve.

Treatment of RION

The treatment for RION is still controversial, but based on the pathophysiology of the disease, the main studies are about the use of hyperbaric oxygen therapy, the use of corticosteroids, anticoagulants, angiotensin-converting enzyme (ACE) inhibitors and, more recently, bevacizumab—a monoclonal antibody to vascular endothelial growth factor (VEGF).[67,68] However, to the date of this report they have only been studied in small series of cases and animal studies. There has been no double-blind randomised study for any of these therapies in RION.[23,69]

Dexamethasone has been used in a dosage of 4 to 10 mg (oral or intravenous) per day, with dose reduction to 2 to 4 mg every 5 to 7 days. Corticosteroids are believed to alleviate radiation toxicity by reducing oedema and corticosteroids can reverse free radical damage, but despite this, although they have demonstrated efficiency in radiation necrosis of the brain, they have not been shown to be of benefit in RION.[7,70]

Anticoagulants (mainly warfarin and heparin) are widely used because they are believed to reduce the damage caused by RT by promoting blood flow to irradiated tissue, both by preventing and repairing small vessel endothelial damage, but also they have no proven benefit.[69,71]

The ACE inhibitor ramipril (used at a dose of 1.5 mg/kg/day for 6 months and started 2 months after RT) may prevent radiation-induced injury by reducing pro-inflammatory cytokines. It was tested in rats exposed to a single dose of 30 Gy and treated early with this drug. There was a protective action on the development of RION when compared with untreated rats, which developed optic nerve demyelination. However, the high cost of the drug and the lack of clear evidence of effectiveness in humans still contraindicate its use.[7,69,72,73]

Hyperbaric oxygenation therapy has been administered with the dive in a 2 atmospheres (atm) chamber preferably initiated within 72 hours from the onset of symptoms for about 20 to 30 sessions in

1 month with each dive lasting about 2 hours.[9,74,75] The effectiveness of this therapy is associated with the relief of radiation necrosis effects by artificially increasing the oxygen tension in affected tissues, stimulating angiogenesis and reoxygenating tissues previously in hypoxia. Its effectiveness in RION is questioned by the high cost and the lack of studies demonstrating efficacy with improvement in only a modest proportion of cases.[69,76] Also, the use of hyperbaric oxygenation requires that the patient is completely free of tumour, given the angiogenesis-inducing activity of this treatment. Common, relatively minor side effects of hyperbaric oxygenation include barotrauma and lenticular myopia, that could persist for months. Rare side effects include seizures and pulmonary toxicity.[7,74]

Bevacizumab (systemic anti-VEGF) has been administered intravenously at 7.5 mg/kg every 3 weeks for 12 months.[77,78] It is believed to reduce radiation necrosis by decreasing capillary leakage and oedema.[77] This drug was proven effective in a randomised clinical study for its use in radiation-related intracranial necrosis, which could justify its use in RION. Also, case reports have reported a significant improvement in visual acuity with its use.[68,69,77,78] It can be administered intraocular (1.25 mg in 0.05 ml every 6 to 8 weeks, at least 2 initial injections), especially in cases of previous RION. A series of case reports, showed improvement of eye examination in all patients and visual acuity in most.[69,79] Adverse effects from systemic administration of bevacizumab are rare and include cardiovascular (hypertension, thromboembolism), CNS (headache, pain syndromes, tumour recurrence), gastrointestinal (abdominal pain, nausea, vomiting, anorexia), haematological (haemorrhage, leukopaenia, neutropaenia), and musculoskeletal (weakness, myalgias) abnormalities.[80–82]

There are therefore limited data supporting any treatment and their use remains limited and potentially unsafe. Bevacizumab shows some promise but the application in practice remains unknown until a treatment can be categorically confirmed to reverse of visual loss caused by RION.[23]

Conclusion

It is evident the need for the medical professional to know and understand the epidemiological basis, as well as to identify the radiation exposure (and the respective dose of exposure), especially when the diagnosis of RION can be confused with other clinical conditions that may have the same symptoms.

Although rare, it brings with its diagnosis a series of factors, which the patient faces together with the medical team, thus requiring multi-professional care. Moreover, even once diagnosed, it has complicated management with few studies to guide how to treat it.

There is a need for more studies on the epidemiology and pathophysiology of the condition and especially a need for randomised double-blind treatment trials. Also there is a need to support the patient that is affected by the disease. Likewise, it is necessary to define with greater precision the risk factors associated with the occurrence of RION, since when addressing any health problem, especially nerve damage, the focus should be on prevention. Thus, determining these factors would aid in the development of safer RT protocols for head and neck tumours in order to reduce the risk of the development of RION.

Declaration of interest statement

The authors report no conflict of interest

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