RADIATION AND THE NERVOUS SYSTEM

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Abstract

Radiation Therapy (RT) is widely used for benign and malignant brain tumours as it is effective and well tolerated. However, damage to the surrounding healthy nervous system tissue leads to a variety of complications both in the short term and long term that range from mild and self-limiting to irreversible and fatal. Radiation neurotoxicity is due to a combination of early inflammation and oligodendroglial damage followed later by brain tissue necrosis, white matter damage, accelerated vascular disease and the development of secondary tumours. This article explains the basic principles of radiation physics, the different modalities that are used in clinical practice, how radiotherapy is planned and delivered and the scientific basis of radiation damage. The main body of the article focusses on the clinical features of radiation toxicity in the brain, spinal cord, cranial and peripheral nerves with an emphasis on the distinction between early and delayed complications.

Key Points

Radiation Therapy (RT) for brain and spinal tumours are most commonly delivered as photons in the form of X-rays or gamma rays. Proton Beam Therapy is used mainly for paediatric tumours to minimise long term toxicity and, in adults, for radioresistant tumours that are near critical structures requiring very high doses.

Precise dosimetry and treatment planning enables clear delineation of tumour treatment targets from Organs at Risk, so as to minimise collateral normal tissue damage.

Radiation toxicity in the brain, spinal cord or plexus can occur acutely but more commonly manifests shortly after the completion of RT (Early Delayed) and is usually reversible. In contrast, Late Delayed RT toxicity is usually irreversible and presents with progressive neuronal loss, leukoencephalopathy and accelerated vasculopathy.

Neurologists will come across acute presentations of RT toxicity months or years after the patient has completed RT including SMART syndrome or radiation vasculopathy presenting as a stroke-like episode, subacute myelopathy and delayed cognitive decline.

Second tumours can develop decades after RT in adult survivors of childhood tumours.

Introduction

Radiation therapy (RT) is used to treat a range of malignant and benign conditions of the brain, skull base and adjacent structures with curative and palliative intent. Treatment can be delivered using a variety of techniques, taking advantage of the specific characteristics of the different modalities and platforms for delivery. The most commonly used modality is external beam radiation with photon therapy, in the form of X-rays or gamma rays. X-ray photon treatments can easily penetrate through tissues and are usually prescribed in daily sessions (fractions) using a linear accelerator, with the total radiation dose being delivered over several weeks. The precise dose-fractionation is dependent on the type of target and clinical indication. Some smaller tumours, such as vestibular schwannomas and meningiomas, can be treated with radiation therapy in a single treatment session (stereotactic radiosurgery, SRS) or a small number of sessions (stereotactic radiotherapy, SRT), while larger tumours such as gliomas require multiple fractions, usually over 3 to 6 weeks. Alternative delivery platforms include Gamma Knife (Elekta, Stockholm, Sweden) or Cyberknife (Accuray, California, USA), which are able to provide more conformal radiation dose distributions to smaller targets. However, techniques for undertaking stereotactic treatments on standard linear accelerator platforms have also been developed and continue to evolve.

Particle therapy, primarily Proton Beam Therapy (PBT), utilises the specific physics associated with the dose deposition of a particle beam in tissue, namely that most of the energy is delivered at the distal end of its range, immediately before the particle comes to rest – known as the Bragg peak. When planned accordingly, this can lead to an increase in dose deposition in the clinical target and minimisation of dose to normal tissues beyond the Bragg peak. There are two main indications for PBT in clinical practice: for dose escalation to radioresistant tumours at sites where standard photon radiotherapy cannot deliver the necessary dose due to the proximity of critical structures, such as skull base chordoma or chondrosarcoma; or to reduce the toxicities of RT to the brain and surrounding soft tissues, particularly in the paediatric, teenage and young adult populations, where the negative effects of irradiating the developing brain are more pronounced.

Mechanisms of radiation damage

Irradiation of tissue causes different types of DNA damage through the production of highly reactive free radicals: single-strand break repair, double-strand break repair, mismatch repair and base

excision repair. However, some lesions fail to repair adequately and it is the accumulation of these lesions that may eventually lead to cell death, either by a programmed mechanism such as apoptosis or autophagy, or via mitotic catastrophe at a future cell division. If the damage does not cause cell death, it may lead to a late manifestation of radiation such as the development of a secondary tumour, which can occur several years or decades after radiation exposure (1).

The precise mechanisms responsible for radiation toxicity of the nervous system are incompletely understood. For example, several processes have been hypothesised to explain radiation-induced neurocognitive decline with a range of preclinical and clinical data to support them. There is evidence of radiation causing a reduction in neurogenesis in the hippocampus, with a depletion of neural progenitor cells occurring over the course of multiple cell divisions in preclinical models. Changes in the cellular microenvironment are also a major factor in the determination of cell fate and reduction in neurogenesis. The oxidative stress induced by radiation results in upregulation of pro-inflammatory pathways and an increase in number of activated microglia, which act as potent inhibitors of neurogenesis. Radiation can also trigger the death of endothelial cells, causing thrombus formation on the exposed matrix and small vessel occlusion. Furthermore, accelerated atherosclerosis and microangiopathy after radiation can lead to vascular insufficiency and infarction (2).

Radiotherapy treatment planning

There are multiple linked processes involved in the planning and delivery of a course of RT. Initially, the patient undergoes CT imaging while immobilised in the treatment position, usually via a thermoplastic head shellDiagnostic MR images obtained previously are co-registered with the planning CT scan and used for delineation of the treatment targets and relevant organs at risk (OARs). This is known as the Gross Target Volume (GTV). Depending on the underlying tumour histology, the radiotherapist will delineate an appropriate margin around the visible tumour to account for possible microscopic infiltration (Clinical Tumour Volume), and a small additional margin is then added to account for small movements that can occur even within the immobilisation device. This final volume is called the planning target volume (PTV). The radiotherapy dosimetrists and physicists create a treatment plan which delivers the prescription dose homogenously to the PTV, whilst ensuring that the OARs do not receive more than the maximum allowed. See **Figure 1** for an illustrative case.

OAR radiation dose constraints are defined from the literature based on clinical and preclinical radiobiological data. Each major structure within the nervous system has a particular dose constraint associated with it, and these constraints are often given greater priority in the radiotherapy planning process than treating the target, meaning that PTV dose coverage is compromised to avoid risk of significant radiation-induced toxicities. For example, the dose constraint to the optic chiasm is 55Gy. Published data reveal that doses in excess of 55Gy lead to an incrementally higher risk of radiation-induced optic neuropathy: <3% at 5 years post-RT when <55Gy delivered, up to 7% at 5 years at 55-60Gy (3).

Radiotherapy dose fractionation

The relationship between radiation dose and cell survival varies between tissues. Cells may be killed by a single lethal radiation hit, or by a succession of sublethal hits. In addition to the overall radiosensitivity of certain tissues, there is also a difference in sensitivity to treatment fraction size. For example, the difference in biological effect of treating to a dose of 20Gy in 10 daily fractions (2Gy per fraction) versus 20Gy in 5 daily fractions (4Gy per fraction) will vary between tissues depending on their sensitivity to fraction size (4). This fraction size sensitivity is most commonly expressed using the alpha-beta ratio, which incorporates a linear component (alpha) of lethal cell kill and a quadratic component (beta) of sublethal cell kill. By fractionating treatment, i.e. splitting the total dose up into multiple smaller radiation doses, it allows for repair to sublethal damage between fractions. This is more effective in normal tissues than in tumour tissue, so fractionating treatment can increase the therapeutic ratio between tumour control probability and normal tissue damage probability. Unlike many tumour cell types, the normal tissues of the nervous system are established as being particularly sensitive to changes in fraction size. Therefore, splitting radiation treatment into multiple fractions over several weeks will facilitate more sublethal damage repair in these normal tissues than if the same overall radiation dose were delivered over a shorter overall treatment time (5).

RADIATION COMPLICATIONS IN THE BRAIN

Early Complications

Acute Radiation Encephalopathy

Acute radiation encephalopathy (ARE) appears within 2 weeks of the start of brain RT and occasionally within hours after the first fraction. The most common symptoms are drowsiness, headache, nausea and vomiting together with a worsening of pre-existing neurological deficits. The main risk factor is the size of the tumour and the dose per fraction (usually > 3 Gy/fraction). It is rarely seen nowadays as dose fractionation is restricted and large tumours are routinely debulked prior to RT. Patients usually recover quickly although herniation and death have been reported. In an older series, ARE occurred in 50% of patients with brain metastases treated with 15 Gy in two fractions (6). As the conventional dose fractionation for Whole Brain Radiotherapy nowadays is either 20Gy in 5 fractions over one week or 30 Gy in 10 fractions over 2 weeks (7), this complication is almost never seen.

Sometimes patients complain of nausea and moderate headache on the evening after the first fraction of RT. Steroids may help especially in patients with large tumours or with considerable oedema particularly at risk of herniation. Where surgical debulking is not possible, these patients should be prescribed dexamethasone 16 mg daily 2-3 days before the first fraction and the dose per fraction ideally limited to 2Gy. The pathophysiology of ARE probably results from radiation-induced blood-brain barrier (BBB) disruption, accounting for a rise in intracranial pressure.

Early-delayed Radiation Encephalopathy

Early-delayed Radiation Encephalopathy is so called as it starts from 2 weeks to 6 months after the completion of RT. The pathophysiology is thought to be due to transient demyelination caused by disruption of the BBB and/or oligodendroglial injury. The most common symptoms include fatigue, drowsiness, lethargy, memory and attentional deficits. At its worst, patients may be asleep for most of the day. Somnolence syndrome, characterised by hypersomnolence, nausea, and anorexia, was first described in children receiving low-dose RT for scalp ringworm and after prophylactic cranial RT for leukaemia; it is less commonly seen in adults. The diagnosis is clinical as neither MRI nor EEG show specific changes. Patients usually improve within a few weeks. There may be a biphasic course with symptoms appearing from days 11-21 and then again from days 31 to 35 (8). As a result, many oncologists continue steroids during and after radiotherapy.

Pseudoprogression

About 6 – 12 weeks after the end of RT, patients may experience worsening of pre-existing neurological deficits leading to the suspicion of tumour progression. Imaging is usually unhelpful as the MRI may show appearances of tumour progression which resolve over the next few months without any specific anti-tumour intervention. This phenomenon is known as 'pseudoprogression' and has been described in up to 30% of patients with glioblastoma treated with concomitant temozolomide and radiotherapy. Ironically, pseudoprogression may be associated with a better tumour response (9). Patients usually improve within a few weeks or months associated with slow radiological improvement. Advanced imaging techniques such as perfusion-weighted imaging and magnetic resonance spectroscopy (MRS) may help in distinguishing between pseudoprogression from true progression but interpretation is limited by the presence of residual tumour within the irradiated area.

Some patients complain of poor attention and memory for up to 6 months following brain RT which reassuringly does not predict the development of long-term cognitive decline. We therefore warn patients who are keen to resume work immediately after RT that they should inform employers about the possibility of a delayed or phased return.

Brainstem syndrome

An early-delayed subacute brainstem syndrome can occur 1–3 months after RT for pituitary or head and neck cancer, where the treatment fields overlap the brainstem. Clinical features include ataxia, dysarthria, diplopia, and/or nystagmus as well as hearing loss. MRI sometimes shows high signal change within the white matter of the brainstem and the cerebellar peduncles which may enhance. This condition usually responds to steroids within a few weeks; very rarely it results in coma and death.

Late Complications

Late complications usually start six to twelve months after the completion of RT but can be delayed by many years or even decades. The two main complications are radionecrosis and late-delayed radiation encephalopathy.

Radionecrosis

Radionecrosis (RN) is the most common late complication and was first described pathologically in 1948 in a series of patients, one of whom had a recurrent 'rodent ulcer of the scalp' (10). It can be difficult to distinguish from tumour recurrence both clinically and radiologically. Nowadays, RN is most commonly seen after focal RT for a brain metastasis but can also occur in patients who have had RT for extracranial and extra-axial tumours, in whom normal brain was included within the radiation field (e.g. head and neck cancer, skull osteosarcoma, pituitary adenoma, clival chordoma). A typical example is bilateral medial temporal lobe necrosis followingRT for pituitary tumours **(Figure 2)** or nasopharyngeal cancer. It is seen less often nowadays due to reduction in dose per fraction and improvements in the delivery of RT.. It is now recognised that the upper limits of a "safe dose" of 55–60 Gy administered to a focal field with fractions of 1.8–2 Gy per day are associated with a less than 5% risk of RN. Patients with vascular risk factors such as hypertension, diabetes and old age are at higher risk of RN, as are those who have concomitant chemotherapy. Some patients without any particular risk factors may develop RN, probably because of increased sensitivity to radiation, such that they develop RN at conventional dose fractionation (11).

RN nowadays is most commonly encountered after Stereotactic Radiosurgery (SRS) e.g. Gamma Knife treatment for brain metastases (5-25% of cases), and also for non-neoplastic conditions such as arteriovenous malformations (up to 20% of cases). Symptoms of RN are indistinguishable from those of tumour recurrence or progression and brain imaging is likewise similar. More recently, an MRI sequence with delayed contrast sequences known as TRAMS (Treatment Response Assessment Maps) or Contrast Clearance Analysis has become routinely available in clinical practice as it is both sensitive and specific (12). It requires the acquisition of two standard 3D T1-weighted MRIs—one 5 minutes and another an hour after injection of gadolinium. The first series is digitally subtracted from the second. The analysis results in high resolution, volumetric maps distinguishing regions of contrast clearance (blue) from contrast accumulation (red). RN shows up as red due to the poor clearance of contrast in non-viable tissue containing irradiated vessels while tumour recurrence shows up as blue due to the rapid clearance through tumour vasculature (**Figure 3)**.

Treatment of RN is with dexamethasone and resection of necrotic foci in refractory cases. Steroid dependence can occur. Other treatments such as bevacizumab, hyperbaric oxygen or drugs such as pentoxifylline, alpha-tocopherol and pentobarbital have also been tried but without clear evidence of efficacy.A recent systematic review concluded that bevacizumab appeared to be more efficacious and just as safe as corticosteroids.(13)

Late-Delayed Radiation Encephalopathy

It has been known for many years that radiotherapy can cause delayed cognitive impairment varying from mild memory loss to a severe dementia (14). This complication is seen more frequently in adult survivors of childhood brain tumours and in patients with low-grade gliomas (LGG) where the tumour remains in prolonged remission for many years (15). MRI shows variable degrees of high T2W signal change in the subcortical white matter and brain atrophy. Some patients deteriorate slowly while the majority remain stable. Cerebral atrophy may also be strikingly focal where specific lobes of the brain have been irradiated. (**Figure 4)** There is no recognized treatment for this syndrome although some authors have advocated the use of anticholinesterases for symptomatic benefit (16).

The long-term cognitive effects of radiotherapy in LGG patients have been reported in a study comparing 195 patients with LGG (of whom 104 had been treated with radiotherapy) with a matched series of patients with low grade haematological malignancies and healthy controls, followed up for at least six years. Patients with LGG experienced significant problems across a range of Health-Related Quality of Life domains, including neurocognitive deficits, but these were associated with tumour changes. Only high dose per fraction (>2 Gy) resulted in significant added cognitive decline (17). Interestingly, the same group published their findings after a follow up of 12 years and found that the patients who had received radiotherapy even at doses less than 2 Gy/fraction showed a progressive decline in attentional and executive functioning and speed of information processing. 53% patients who had radiotherapy developed cognitive deficits in at least five of 18 neuropsychological test parameters compared with 27% patients who had not received RT (18).

Whole Brain Radiotherapy (WBRT) was the standard treatment for Brain Metastases until the last decade and causes cognitive decline in more than 60% of patients within 2-6 months after treatment. It has now been replaced by Stereotactic Radiosurgery (SRS) for fit patients with stable or controlled extracranial disease and a reasonable prognosis from their underlying cancer (at least six months). (19). Hippocampal sparing techniques are gaining in popularity for patients with Brain Metastases who are not suitable for treatment with SRS but have not yet been shown to provide a consistent cognitive advantage

In patients with Primary CNS lymphoma who have been traditionally treated with combined high-dose intravenous methotrexate chemotherapy followed by WBRT, the incidence of severe cognitive impairment increases with age, reaching 83% in patients over 60 years (20). Based on the results of a

randomized phase 2 study by a European consortium (the IELSG-32 study), the Standard of Care across Europe for fit patients with PCNSL under the age of 70 years is now a chemotherapy regimen known as MATRix (Methotrexate, Ara-C, Thiotepa and Rituximab) followed by Autologous Stem Cell Transplantation, a strategy that avoids the use of WBRT altogether thus reducing potentially fatal neurotoxicity (21).

Radiation-Induced Secondary Normal Pressure Hydrocephalus

Radiation-Induced dementia is characterized by a "subcortical dementia" pattern associated with diffuse white matter injury, usually starting within 2 years of treatment. Patients present with a similar picture to Normal Pressure Hydrocephalus and develop progressive memory loss, reduced attention, gait difficulties, urinary incontinence and fatigue. There may be emotional lability and apathy which is difficult to distinguish from depression. Antidepressants are frequently tried but do not improve cognitive function. Eventually, patients may develop akinetic mutism. MRI shows ventricular enlargement, diffuse confluent subcortical white matter change and cortical and subcortical atrophy and

There is no specific treatment for radiation-induced dementia. However, ventriculoperitoneal shunting is sometimes tried with incomplete and short-lived improvement (**Figure 5**) (22). Deterioration occurs in about 80% of cases and death generally occurs within four years after the onset of the disorder.

Radiation-induced brain tumours

Irradiated patients are more prone to developing second brain and spine tumours than the general population. Meningiomas (70%) (**Figure 6)**, gliomas (20%) and sarcomas (10%) are the most common tumours and develop many years (mean onset 12 years) or decades after treatment. In a study of over 10,000 patients treated for *Tinea capitis* with low-dose (1.5 Gy) radiation, the relative risk for all tumours was 6.9 and the risk for glioma was 2.6 (23). This has been confirmed in a number of other studies. In patients treated for childhood acute lymphoblastic leukaemia, the relative risk is so high (22) as to justify screening MRI brain imaging for adult survivors (24).

In order to diagnose a radiation-induced tumour, there has to be a long interval between the treatment and the occurrence of the second tumour (cases up to over 60 years later have been

described), the tumour has to grow within the radiation field or at its margins and be of a different histological subtype to the primary tumour. The prognosis of these tumours is poor as these patients have limited reserve for further radiotherapy, although the longer the gap between the original treatment and the secondary tumour, the more scope there may be due to normal tissue recovery.

Radiation-induced vasculopathy

Radiation can damage the intracranial vasculature leading to ischaemic stroke or haemorrhage. The carotid artery can become stenotic after radiotherapy to the neck for lymphomas or head and neck cancers, and occasionally can rupture a few weeks after RT causing death. Late-delayed complications are however more frequent, and generally occur many years after treatment (median time about 20 years for extracranial arteries, 7 years for intracranial arteries). Radiation induced vasculopathy is an accelerated form of atherosclerosis, and often occurs in unusual locations e.g. the distal internal carotid artery. It has recently been described within two years of Proton Beam Therapy for childhood brain tumours (25). The lesions consist of one or more arterial stenoses or occlusions of the carotid or cerebral arteries within the radiation portal. Pathologic findings include destruction of the internal elastic lamina and replacement of the normal intima and media with fibrous tissue. Treatment includes management of vascular risk factors and, where appropriate, carotid endarterectomy. However, surgery may be more difficult because of vascular fibrosis and poor wound healing. If a stroke is identified in a patient who has had previous RT, it should not be assumed to be due to radiation vasculopathy unless it is within the radiation portal and other risk factors should be sought.

Moyamoya Disease

Moyamoya disease is a progressive occlusive cranial vasculopathy characterized by abnormal anastomoses and netlike blood vessels at the apices of the intracranial internal carotid arteries, the proximal anterior cerebral arteries and middle cerebral arteries (26). It results in decreased cerebral blood flow with an increased risk of stroke, transient ischaemic attacks and focal seizures. It is often seen in patients who had intracranial RT as young children, particularly those treated for optic chiasm glioma, a condition often associated with neurofibromatosis type 1, which is a risk factor for vasculopathy in itself. The strong association between NF-1 and moyamoya is one of the reasons why radiation has been replaced with chemotherapy in younger children with optic pathway gliomas. Treatment is aimed at prevention of further strokes through surgical revascularization procedures.

Radiation-Induced Cavernomas, Angiomatous Malformations, and Aneurysms

Vascular malformations such as telangiectasias and cavernomas are increasingly being recognised as a long-term complication of brain radiotherapy, due to the routine inclusion of gradient-echo and susceptibility weighted sequences in modern MRI protocols. When present, their main risk is intracranial haemorrhage but this is rare (27). There have been occasional cases of radiation-induced intracranial aneurysms reported with fatal outcomes.

SMART syndrome

SMART syndrome (Stroke-like Migraine Attacks after Radiation Therapy) is a poorly understood late complication of brain RT for both primary and secondary brain tumours. It presents with a combination of migraine-like headaches and cortical dysfunction including seizures and focal neurological deficits e.g.g aphasia, neglect and hemiparesis. Seizures may be prolonged and poorly responsive to anti-seizure medication. Steroids do not seem to help. It has a distinctive radiological appearance (**Figure 7**) with pial enhancement and cortical high signal change within the radiotherapy field. It is now recognised that neurological deficits can persist even after radiological improvement (28). There is ancecdotal and imaging evidence (CT perfusion) that SMART syndrome is caused by reversible hemispheric hypoperfusion (29) but the aetiology is unknown.

RADIATION COMPLICATIONS IN THE SPINAL CORD

RT damages the cord in much the same way as the brain although is less commonly encountered, due to the relative rarity of spinal cord tumours compared to brain tumours. However, the spinal cord is a critical Organ at Risk in the planning and delivery of RT for non-CNS tumours, including head and neck and paravertebral cancers. Early and late-delayed myelopathy, lower motor neurone disorder, and spinal haemorrhage have all been described.

Early-Delayed Radiation Myelopathy

This usually follows radiation to the cervical or thoracic cord, most commonly seen after mantle RT for Hodgkin's Disease within the cervical cord. The clinical symptoms include Lhermitte's sign, presumably caused by transient demyelination in the posterior columns, secondary to a loss of oligodendroglial

cells. There is no specific treatment for this condition and recovery is the norm. It is important to reassure patients that this does not evolve to a progressive myelopathy.

Late-Delayed Radiation Myelopathy

Late-Delayed Radiation Myelopathy (DRM) occurs 1 to 10 years after exposure to RT and, as with brain neurotoxicity, risk factors include older age, total RT dosage (above 60 Gy), higher dose per fraction and the volume of cord irradiated. DRM presents with a combination of slowly progressive sensorimotor deficits, often a hemicord (Brown-Sequard) syndrome, with bladder involvement eventually leading to paraparesis or tetraparesis. MRI may be normal initially but usually the cord becomes swollen and, in about 50% of cases, there is gadolinium enhancement. Eventually there is cord atrophy with occasional cystic cavitation. The diagnosis can only be made if the cord signal change lies within the radiation-exposed area and if all other potential causes of myelopathy have been excluded. The natural history varies - in some patients, the symptoms stabilise, in others they progress to a complete deficit.

Neuropathological findings include demyelination, focal necrosis, and axonal loss, together with fibrinoid necrosis of the vessel walls, perivascular fibrosis and sometimes vasculitis.

Corticosteroids are useful in the subacute stages to reduce the inflammatory component of the disorder; however, patients often become steroid-dependent and only a few experience long term improvement. There is no current proven treatment although hyperbaric oxygen and anticoagulation have both been tried in small series.

RADIOTHERAPY COMPLICATIONS IN THE CRANIAL NERVES

Late-delayed complications of RT in the cranial nerves arise in fewer than 1% of cases after conventional radiotherapy (60 Gy in 2 Gy daily fractions). Having said that, patients who have previously received greater than 50 Gy to the posterior fossa have a higher likelihood of developing hearing impairment. Current radiotherapy planning techniques allow for this risk to be minimised.

Optic nerve

The most clinically important cranial nerve implicated in delayed radiation toxicity is the optic nerve which can be damaged many years after treatment for orbital, pituitary or suprasellar tumours. The Optic Nerve apparatus is regarded as a major Organ at Risk when planning treatment to nearby targets. RT-induced optic neuropathy usually presents with subacute painless visual loss, progressing to monocular or binocular blindness with optic atrophy. Fundoscopy of anterior lesions shows papilloedema and peripapillary haemorrhage, sometimes associated with radiation-induced retinal lesions, but is usually normal in posterior lesions. MRI of the anterior visual pathways with fat saturation is useful in these cases showing enlargement and signal change in the optic nerve and chiasm, with contrast enhancement.

As with DRM, steroids are useful in the acute setting but there are no proven treatments for progressive optic neuropathy. Optic nerve sheath fenestration has been used in a few patients with some success (30).

Oculomotor nerves

Transient sixth nerve palsy may occur following radiation to the pituitary gland and cavernous sinus and very occasionally after treatment of nasopharyngeal carcinoma. Neuromyotonia has also been reported, characterized by spontaneous eye muscle spasm and intermittent diplopia, usually lasting a few seconds, occurring up to several times an hour. This may respond to phenytoin or carbamazepine.

Trigeminal nerve

Facial numbness due to trigeminal neuropathy has been reported after radiosurgery for trigeminal neuralgia, trigeminal and vestibular schwannomas.

Facial nerve

Aguesia is commonly reported by patients irradiated for head and neck cancer. Facial motor neuropathy is almost never seen after fractionated RT and should prompt suspicion of perineural invasion. Facial palsy following stereotactic radiosurgery for vestibular schwannoma is seen in less than 5% of cases.

Vestibulocochlear nerve

Early delayed hearing loss is usually due to otitis media, caused by oedema of the eustachian tube and temporary build-up of fluid within the middle ear. In contrast, late onset hearing loss due to cochlear damage is characterised by high-frequency hearing loss and tinnitus.

Lower cranial nerves

The glossopharyngeal, vagus, spinal accessory and hypoglossal nerves can all be damaged by large radiation doses for head and neck cancer and typically arise months to years after treatment. The hypoglossal nerve is the most commonly involved nerve presenting with unilateral asymptomatic or bilateral disabling paralysis with tongue atrophy. Unilateral vocal cord and palatal palsy gives rise to dysarthria and dysphagia. Spinal accessory nerve palsy presents as painless shoulder drop.

Dropped head syndrome has been described as a potential late-delayed complication of RT due to weakness of the neck extensors several years after irradiation involving the cervical region, e.g. mantle RT for Hodgkin's Disease. The differential diagnoses include myasthenia gravis, motor neurone disease or isolated neck extensor myopathy. Such extensive radiotherapy fields are much less commonly used today.

RADIOTHERAPY COMPLICATIONS IN THE PERIPHERAL NERVES

Plexopathy

Brachial and lumbosacral plexopathies are the most important late-delayed complications of RT in the peripheral nervous system but are rarely seen nowadays, with the use of smaller doses and a greater awareness of the long-term effects of RT. Brachial plexopathy is the more common and occurs after RT to the supra-, infraclavicular or axillary nodes, usually for breast cancer and sometimes Hodgkin's Disease. Lumbosacral plexopathy is much less commonly seen after RT for pelvic or lower abdominal and pelvic cancer (uterus, ovary, cervix, testis, rectum, or prostate).

Occasionally, patients can present with an early-delayed plexopathy within a year of treatment, which usually improve within a few months, thought to be due to direct radiation toxicity on the Schwann cells inducing demyelination. This responds to steroids **(Figure 8**).

Late-delayed radiation plexopathies appear 3-20 years after treatment. As with other RT toxicity, the most important risk factors are total radiation dose (> 60 Gy) and dose per fraction (> 2 Gy), the use of overlapping fields and combined chemo-radiotherapy. There are two phases in the pathophysiology: during the first phase, direct radiation damage to the nerves causes acute inflammation which then resolves; later on, there is injury to the small arterioles and perineural fibrosis accounting for the severe and irreversible nerve damage.

Initial symptoms include distal paraesthesiae and dysaesthesiae, muscle weakness and atrophy confined to specific myotomes, dermatomal sensory loss and early loss of reflexes. The lack of pain and myokymia, when present, is highly suggestive of the diagnosis and helps differentiate from malignant infiltration of the plexus. There may also be visible skin complications such as radiation dermatitis, painful induration of the axillary region, and/or lymphoedema. During the later stages, there is progressive motor loss varying from localised muscle weakness to an almost complete paralysis of the limb.

Neurophysiology shows normal motor and sensory conduction velocities. F waves may be absent or delayed. Electromyography shows fasciculations, fibrillations and positive sharp waves. The most important neurophysiological finding in favour of radiation-induced plexopathy is the presence of myokymic discharges, present in about two-thirds of patients, but almost never seen in tumour infiltration. MRI is the imaging modality of choice in differentiating between radiation fibrosis, seen as thickening of the brachial plexus, with occasional contrast enhancement and tumour infiltration, seen as nodular mass lesions along the branches of the brachial plexus (**Figure 9**). Rarely, MRI is inconclusive, and a biopsy may be indicated. In radiation plexopathy this reveals fibrosis and the absence of tumour infiltration.

Treatment is supportive involving physiotherapy, lymphoedema massage and bandaging and pain management.

Lower motor neuron syndrome

A lower motor neuron syndrome resembling Motor Neurone Disease has been described after RT to the distal spinal cord and cauda equina, mainly as treatment for testicular cancer and lymphoma. It presents with progressive proximal and/or distal symmetrical leg weakness associated with muscle fasciculations and wasting with normal sensory findings (31). Sphincter disturbance and sensory loss may appear much later. MRI is usually normal, but contrast enhancement of the roots of the cauda equina has been described. The CSF is usually acellular, with high protein levels. EMG reveals denervation with preserved sural action potentials. This is best regarded as a motor neuronopathy rather than a radiculopathy based on the neurophysiology.

Radiation-induced malignant peripheral nerve sheath tumours

Radiation-induced nerve malignant peripheral nerve sheath tumours (MPNST) have been reported 4 to 41 years after RT, particularly in patients with neurofibromatosis type 1 (NF-1). Patients complain of localised pain followed by sensorimotor deficit and diagnosis is made on imaging. Treatment is surgical complete resection of the tumour. The prognosis of these MPNST is worse than that reported for de novo MPNSTs (32).

CONCLUSION

It is important for neurologists to be aware of the multiplicity of early and delayed manifestations of radiotherapy neurotoxicity, as patients may present both to acute neurology and stroke services and to neurology out-patient clinics. The diagnosis of radiation-induced neurotoxicity should only be made however if the anatomical region lies within the radiation portal and is biologically consistent with what is known about the mechanisms and timing of radiation damage. Treatment options are limited for these complications and therefore knowledge of treatment modalities other areas of neurology such as neurodegeneration are essential to improve patient Quality of Life.

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RADIATION AND THE NERVOUS SYSTEM

Figure Legends

Figure 1: Radiation Treatment Planning

CT scan of patient with right temporal glioblastoma. A - Volume delineation of target and organs at risk (OARs): brown = postoperative tumour bed and residual enhancing gross tumour (GTV); yellow = clinical target volume (CTV), area at risk of microscopic disease infiltration, defined as GTV + 2cm for glioblastoma, edited off barriers to spread (e.g. bone); red = planning target volume (PTV), CTV + geometric 3mm margin for positional inconsistencies within immobilisation device; pink = optic chiasm; dark green = 3mm margin around chiasm for positional inconsistencies; orange = brainstem; light green = 3mm around brainstem for positional inconsistencies. B – Radiotherapy dose distribution >50Gy: prescription dose to PTV of 60Gy. Note compromise of PTV dose coverage medially due to the location of the brainstem and optic chiasm. This radiotherapy plan was designed to ensure that no dose >55Gy was delivered to these critical OARs.

Figure 2: Radiation Necrosis

37 year old patient presenting with severe amnesia 4 years following Proton Beam Therapy for a pituitary adenoma. Axial T2W (Fig 2a), T1W + gad (Fig 2b) images showing bilateral temporal signal change and oedema with irregular enhancement in medial temporal lobes, typical of radiation necrosis. There was no improvement with steroids and the patient remained severely incapacitated by fatigue and amnesia.

Figure 3: TRAMS (Treatment Response Assessment Maps)/Contrast Clearance Analysis maps

Contrast-enhanced T1-weighted MRI (T1-Gd, top) and the calculated TRAMS image (bottom) of a patient with a malignant melanoma brain metastasis receiving SRS. Prior to SRS (left) the enhancing lesion on T1-Gd appears blue in the TRAMS scan. Follow-up MRI 10 months post SRS (right) shows significant shrinkage of the enhancing lesion on T1-Gd, appearing red, suggestive of Radiation Necrosis.

(Courtesy of Prof Yael Mardor, Sheba Medical Centre, Israel)

Figure 4: Delayed Radiation Encephalopathy

55-year-old patient treated with bifrontal parallel fields to a right frontal glioma in 1997, presenting with progressive cognitive and behavioural decline 25 years later. Sagittal (Fig 4a) and Coronal T1W (Fig 4b) shows striking bifrontal and perisylvian atrophy with relative preservation of the parietal and occipital lobes. Note the enhancing residual tumour.

Figure 5: Secondary Normal Pressure Hydrocephalus

66-year-old with left occipital glioblastoma treated with concomitant chemoradiation. Within a year of radiotherapy (54Gy in 30 fractions) she became increasingly unsteady due to an apraxic gait with urinary incontinence and mild memory loss. Her condition improved with VP shunting but the improvement was short-lived and she died of progressive disease 9 months later.

Coronal T1W post Gd immediately after radiotherapy (Fig 5a) demonstrating normal ventricular dimensions and one year later (Fig 5b) showing dilatation of posterior horns and IVth ventricle and sulcal effacement. Note tumour recurrence around the left lateral ventricle with surrounding oedema.

Figure 6: Radiation induced meningiomas

48-year-old patient who had a pineal germinoma treated with whole brain radiotherapy thirty years previously presenting with new onset generalised seizures. Coronal contrast enhanced T1W image shows two meningiomas both within the midline, one arising from the falx and one from the tentorium with no evidence of tumour recurrence.

Figure 7: SMART syndrome

68-year-old patient with a previous history of left frontal astrocytoma treated with RT 8 years previously. He then presented with a rapid onset of continuous focal motor aware seizures, loss of speech and right hemiparesis that gradually improved over the next three months, leaving him with moderate dysphasia and mild hemiparesis. There was no response to high dose intravenous corticosteroids. Imaging at the onset shows swollen left hemisphere with diffuse high signal and sulcal effacement on axial T2W (Fig 7a) and pial enhancement (Fig 7b)) with high relative Cerebral Blood Volume

on Perfusion weighted imaging (Fig 7c). The appearances had resolved and returned to baseline three months later (Figs 7d and 7e).

Figure 8: Early Delayed Lumbosacral Plexopathy

73-year-old patient with prostate cancer 4 months after completion of radical radiotherapy presenting with subacute distal lower limb oedema, bilateral foot drop and loss of distal sensation. EMG was more suggestive of a lumbosacral plexopathy rather than a sensorimotor neuropathy. Motor function improved completely with steroids although a year later, there was persistent sensory impairment distally.

Axial (Fig 8a) and coronal (Fig 8b) T1W post Gd scans of lumbosacral spine shows diffuse contrast enhancement in the proximal L5 nerves, more on the left (arrow), in the lumbosacral plexus and the proximal S1 roots, again more on the left consistent with an early-delayed lumbosacral plexopathy

Figure 9: Radiotherapy-related plexus changes vs Malignant Infiltration

Fig 9a – Radiation plexopathy. Coronal T1w (A) and STIR (B) MR images of the brachial plexus demonstrating STIR hyperintense signal changes predominantly involving the divisions and cords of the left brachial plexus with mild associated distortion and loss of the perineural fat planes (arrowheads). Note the pleural thickening and adjacent parenchymal scarring within the left lung apex (short arrows) secondary to previous radiotherapy.

Fig 9b – Malignant Infiltration. Coronal STIR (A) and fat-suppressed post-contrast T1w (B) MR images of the brachial plexus demonstrating nodular thickening and enhancement of the right brachial plexus (arrowheads) and adjacent supraclavicular lymphadenopathy (curved arrow) consistent with metastatic infiltration in a patient with known breast carcinoma.

(Courtesy of Dr Sachit Shah, Consultant Neuroradiologist, National Hospital for Neurology and Neurosurgery)

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