Section: Radiation Oncology

Original Research Article

ASSESSMENT OF DEMYLINATION AFTER RADIOTHERAPY IN HEAD AND NECK CANCER PATIENTS

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ABSTRACT

Background: Cervical Spinal cord is considered an important Organ at risk while Radiotherapy of head and neck cancer (HNC). Thus when the tolerance dose is exceeded for spinal cord it is important to look for symptoms of demyelination. **Objective:** To assess post radiotherapy demyelination of Spinal cord in HNC Patients in whom tolerance dose for spinal Cord were exceeded.

Material & Methods: This prospective observational study was conducted on 485 patients receiving radiotherapy for treatment of HNC. In patients whom the doses for spinal cord exceeds tolerance dose of 50 Gy were then assessed for demyelination. Patients showing symptoms of demyelination were examined and Magnetic Resonance Imaging (MRI) to assess extent of damage was obtained and conservatively managed.

Results: Only 80 patients received dose greater than 50 Gray (Gy) to more than 10 cm length of spinal cord. Of these 12 patients developed demyelination which was confirmed on MRI and managed conservatively with Vit.B12 supplementation and pregabaline. Among these10 patients recovered while 2 patients had irreversibly damaged cord. Main reasons for exceeding tolerance dose include locally advanced disease extending to posterior triangle in 80 % patients, progression of disease in 10 % which required additional doses to the gross tumor and Positive margins in 10 % patients for which additional boost doses needed to be delivered.

Conclusions: Demyelination is a debilitating late sequel of Radiotherapy and adversely affect quality of life of the patient and care should be taken while planning radiotherapy so that tolerance doses are not exceeded.

Keywords: Radiotherapy, Demyelination, Spinal cord, Myelopathy, Head and Neck cancer.

INTRODUCTION

The Head and neck cancer (HNC) poses a difficult challenge to healthcare and with around 660000 new cases and 325000 deaths annually worldwide.[1] It is also one of the most common malignancy in India accounting for 30-40% of the new cases.[2] In developing countries like India managing HNC poses a very difficult challenge to healthcare providers as most of the patients report in advanced stage. Radiotherapy forms the mainstay of treatment along with surgery in management of Head and Neck cancers. During Radiotherapy planning of head and neck cancers, several organs at risk (OAR) include salivary glands, trachea, eyes, optic nerve and spinal cord amongst others. With advancement in treatment delivery techniques in past few decades, the inadvertent damage to the vital structures surrounding the primary target lesion site could not be prevented. Spinal cord is an important OAR when treating head and neck cancer patients, being serial organ damage to any part may result in severe dysfunction of which may manifest in form of lot of symptoms but mainly in form of demyelination which is one of the troublesome and major late sequel of Radiotherapy to HNC.

Demyelination means loss of this myelin sheath which forms insulation around nerves.[3] Myelin was first discovered in 1854 by Rudolf Virchow.4 Myelin plays pivotal role in the functioning of Nervous system. Myelin is rich in Lipid and engulfs the nerve fiber which leads to increased velocity of inter-neuronal electrical communication. The process of development of myelin sheath is called Myelinogenesis/ Myelination. Reverse of this process, i.e., myelin degeneration is called Demyelination.[3] Development of myelin occurs from Glial cells in Central nervous system (CNS) and Schwann cells in Peripheral nervous system (PNS). Myelin decreases the capacitance of the axonal membrane thus increasing the rate at which electrical impulses pass via the axons.

Demyelination can present with varied symptoms depending on the affected neurons. Commonly noticed symptoms include central visual field defects like blurriness, double vision, cognition defect, movement or balance disorder, auditory problems, heat sensitivity, speech impairment, tingling or numbness, loss of bowel/bladder control etc. Lhermitte's phenomenon/Syndrome (LS) is a short, intense electrical shock like sensation passing below from the neck via spine to body and limbs, seen as a common sign of demyelination injury.[5]

Due to widespread use of Radiotherapy in the management of HNC and owing to the radio-sensitivity of the spinal cord, these demyelination damages are bound to happen, especially when inadvertent delivery of dose higher than tolerance level or to a longer segment of the cord included in the treatment field especially spinal cord in cervical region is most commonly affected.[6] Symptoms may develop after sometime ranging from 6 months to 2 years later.[7] Thus we aim to assess the incidence of demyelination and its symptoms in HNC patients in which the tolerance dose was exceeded for cervical spine during radiotherapy.

MATERIALS AND METHODS

This is a prospective observational study including 485 patients of HNC who have received Radiotherapy as treatment from January 2019 to December 2019.After taking informed consent from the patients, their hospital records were assessed to look for the dose of radiation received by the spinal cord. All the patients were treated on Theratron 780C Co-60 based machine using 2D conventional radiotherapy technique radiation was used and given in divided doses of 30-35 fractions using Co-60 based 2D conventional radiotherapy technique .Appropriate doses as per indications were given Ranging from 60 Gy to 70 Gy at 2Gy/fraction over five days a week for 6-7 weeks. Then Mean Maximum dose of radiation to the spinal cord was calculated using the ONCENTRA V.2 treatment Planning system for all the patients. Also the mean of length of spine receiving the dose above tolerance level was measured. The patients in whom the tolerance dose of 50Gy to spinal cord exceeded were then patients were followed regularly from 6 months till completion 2 years.

During follow-up, thorough neurological examination was conducted on these patients and those who presented with positive symptoms for demyelination of cord were then taken for MRI (1.5Tesla) to confirm demyelination. After confirmation they were managed medically using Vitamin B12 and Pregabalin.

RESULTS

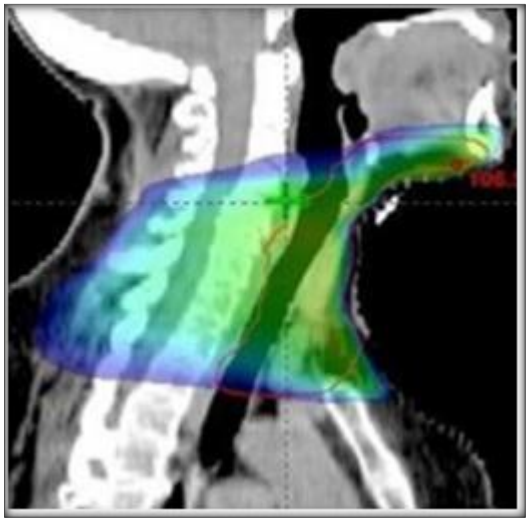

Figure 1: Sagittal view for one of the patient's radiotherapy plan showing 50Gy to the spinal cord with 12.88cm length spine irradiated

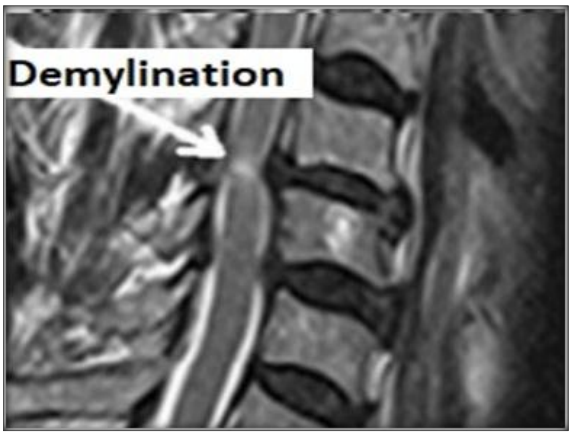

Figure 2: Cervical spine T2 weighted images showing small intramedullary area of cervical cord at C2-C3 level, represent demyelination

Table 1: Total number of Patients, Range maximum dose to spinal cord, length of spinal cord irradiated and patients developing demylination in patient exposed to radiation dose above tolerance level

No. of patients	Range of Max dose received by spinal cord (Gy)	Mean maximum Dose Received by spinal cord	Total dose delivered Gy/ no. of fractions	Mean length of cord received ≥ 50 Gy (cm)	Patients having demyelination symptoms	Reversible/ irreversible demylination
31	50-52	51.25	60/30	10.78	0	
25	52-54	53.4	66/33	12.04	2	
10	54-56	54.6	66/33	14.37	7	1Reversible
14	56-58	56.8	70/35	12.88	9	2 irreversible, 7 reversible

Table 2: Factors increasing demyelination risk

Factors	Factors for increased risk of injury
Exposed radiation dose	Large total dose
Single fraction dose	Dose per fraction > 200 cGy
Organ proportion	Higher volume, e.g. whole-organ radiation
Patient factor	Co-morbidity e.g. hypertension, diabetes
Beam property	High LET radiation

DISCUSSION

Spinal cord is one of the most important organs at risk in HNC treatment with Radiotherapy. The radiation induced toxicities in spinal cord may manifest in form of demyelination. Demyelination post radiation is a rare but serious side effect of Radiotherapy which may be easily missed as it usually develops from 6 months to 2 years after the completion of treatment.6and symptoms are usually transient. LS a type of benign form of myelopathy and results from the demyelination of the sensory neurons due to probable inhibition of oligodendrocyte proliferation after radiotherapy treatment and other symptoms include generalized weakness, stiffness numbness of extremities etc. Etiopathogenesis for the same is inconclusive but it is thought to be due to the damage of vascular endothelium resulting in coagulation and fibrinoid necrosis.[8]

Cervical spinal cord being extremely radiosensitive gets affected the most, especially when exposed to a higher dose of radiation (above tolerance level). This results in damage to myelin sheath of posterior and lateral column (mainly) of the cord. This tolerance level depends on various factors like treatment related factors time duration, quality of radiation given, total calculated dose, dose given per fraction, various host factors include age, co morbidities like hypertension, Diabetes, endocrinological diseases, developmental defects and vascular disorders and adjunctive therapies like concurrent administration of chemotherapy are included.[9,10] Table 2 shows various factors which increase the risk of Demyelination.

In studies done by Fein et al,[11] in patients who received doses ≥50 Gy to spinal cord, LS developed in 8% of patients while in those who received <50 Gy e the incidence was only 3.3%. They also reported that daily doses exceeding 2 Gy per fraction are associated with increased incidence of LS .Similarly Leung et al,[12] in their study, found a correlation between dose and incidence of LSand reported when the total dose to the cervical spinal cord exceeded 48.9 Gy incidence of LS has increased. It is also considered that spinal cord is protected by toxic effects of chemotherapy by the Blood brain barrier. Concurrent chemotherapy administration along with radiotherapy may disrupt the BBB and increase the effect of chemotherapy on the spinal cord.[13,14]

The incidence of LS is around 3.63 and 13% as reported in available literature,[11,12,15] however the incidence in present study was it found to be around 15%(12/80) which may be due to use of 2D conventional radiotherapy and most of the patient presenting in locally advanced stage requiring bigger treatment fields and higher doses. Also all the patients who developed LS received concurrent chemotherapy with Injection Cisplatin may also be a possible reason for the increase in the number of patients.

Clinical evaluation presents with difficulty of being non-specific and hence MRI plays a critical role in confirming the diagnosis and thus aids in proper management. MRI findings suggestive of positive demyelination includes, cord swelling/oedema (decrease intensity on T1 images and increase intensity on T2 MRI images). Prognosis mainly depends on the extent of cord involved in receiving radiation and at which level.[18]

Treatment is mainly conservative and palliative involving Vitamin D3 supplementation which has proven to be effective in recovering from demyelination defect as these patients to develop Vitamin D deficiency. Another vitamin with similar efficiency is Vitamin B12 which is mandatory for development and proper functioning of myelin sheath. It strengthens the Myelin sheath and its deficiency has been correlated with demyelination disorders and impaired myelin repair.[17]

CONCLUSION

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