Radiation Toxicities in Paediatrics

Dr Neeraj Jain
MBBS,DNB,MNAMS,FICRO,PhD
Professor Radiation Oncology
Sri Guru Ram Das University Of Health Sciences, Amritsar
President NZAROI, Sr Vice President AROI

Late Toxicity of Radiation

- Neuro-cognitive Effects and Other Effects on CNS
- Effects on Sexual and Reproductive Function
- Endocrine effects
- Effect on Bone and Soft Tissue and Growth Defects
- Effect on Vision and Hearing
- Risk of second Malignancy

Introduction

- Despite its demonstrable effective therapeutic ratio in children, the use of radiation therapy in children and young adults has been limited by concerns for acute and late effects.
- The inappropriate estimation of the morbidity of the application of local therapy may have severe consequences and thus lead to therapy omission and premature treatment failure or even death.
- A thorough knowledge of the implications of radiation therapy should be carefully considered and be guided by a combination of multidisciplinary experiences and strong objective literature review.

CNS Toxicity

- All forms of ionizing radiation, ranging from nearly weightless photons to particles such as protons or carbon ions, have the potential to produce toxicity in the central nervous system (CNS) .
- Ionizing radiation can damage tissues through direct and indirect effects, either by directly affecting DNA or by inducing radiolysis of cellular water which generates free radicals that harm DNA and cause Metabolic Stress to which Nerve Cells are susceptible.
- The etiology of CNS dysfunction in patients after irradiation is multifactorial influenced by age, comorbidities, psychological and genetic predispositions, characteristics of underlying malignancy

CNS Toxicity

The risk of radiation-induced brain injury depends on the

- Dose (either total dose or per fraction)
- Duration of treatment
- Volume of normal brain irradiated
- Other Treatments

CNS Toxicity

- **ACUTE (Few Days after Radiation)**

Neurologic changes, cerebral edema, seizures, altered level of consciousness, persistent headache, hemiplegic symptoms, hallucinations, and visual disturbances

- **EARLY DELAYED (Weeks/Months after Radiation)**

Radiation somnolence syndrome (prolonged periods of sleep, irritability, fever, nausea, vomiting, cerebellar ataxia, anorexia, dysphagia and dysarthria, and headaches

- **LATE DELAYED (Several Months/Years after Radiation)**

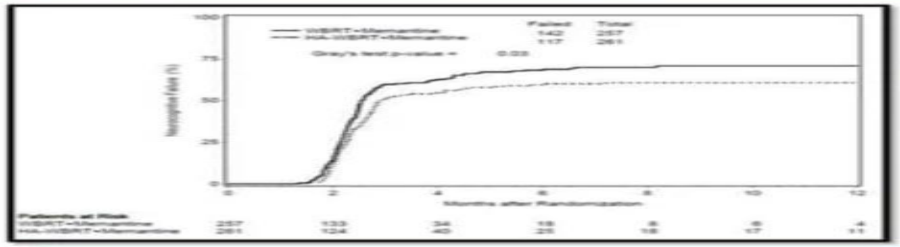
Vascular abnormalities, demyelination

CNS Toxicity

- Pediatric patients have a significant risk for neurocognitive impairment related to brain radiotherapy
- Cognitive dysfunction is well described after radiation therapy and is likely related to effects on the brain during the developmental period.
- Indeed, young age at the time of treatment has been reported as an important risk factor in multiple prospective studies .
- Different mechanisms are reported for the radiation-related neurocognitive impairment, including white matter and brain plasticity changes, vascular damage resulting in chronic ischemia, or decreased neurogenesis
- Evidence is increasingly emerging that proton beam radiotherapy appears to decrease the incidence and severity of late effects, suggesting that this method may therefore be particularly indicated in the treatment of pediatric tumors.

Hippocampus Constraint

HIPPOCAMPUS AVOIDANCE +MEMANTINE + W



Supports the hippocampus as a cognition-specific organ at risk for all forms of brain irradiation

Phase III Trial NRG Oncology CC001

Conformal avoidance of the hippocampal dentate gyrus using IMRT during WBRT plus memantine preserves cognitive function in brain metastasis patients For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 mo. or longer, hippocampal avoidance using IMRT should be considered

VINAI GONDI/ASTRO ABSTRACT/2018

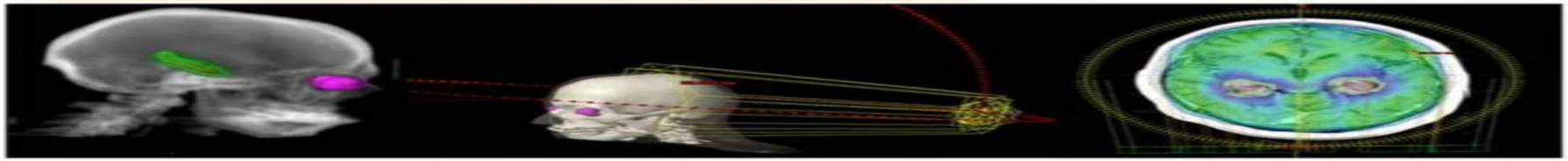
4th MAY 2019/BRAIN

ONCOLOGY EDUCATIVE CARTOON/SLIDE -BY DR KANHU CHARAN PATRO, IMAGES & DATA- GOOGLE

CONSTRAINTS FOR HIPOCAMAPAL AVOIDA

DOSIMETRIC RECOMMENDATION FOR HA WBRT

1. Dmedian < 7.8 Gy,
2. D100% < 10 Gy
3. Dmax < 15.3 Gy)
4. For patients with brain metastasis and expected survival greater than 6 months.



Tomas Kazda /BioMed Research International/2018

3rd NOVEMBER 2019/BRAIN

ONCOLOGY EDUCATIVE CARTOON/SLIDE -BY DR KANHU CHARAN PATRO, IMAGES & DATA- GOOGLE

CNS Toxicity

- Stroke-like migraine that attacks after radiation therapy (SMART) syndrome is a late and delayed complication of radiation-induced brain injury
- The most common symptom is a headache followed by seizures and stroke-like symptoms, such as homonymous hemianopsia, hemiparesis, aphasia, sensory defects, seizures, and migraine-type headaches
- The onset of symptoms after radiation treatment is variable; some cases have been reported after 30 years
- Risk factors are male sex, young age, tumors originating primarily in the central nervous system or metastatic lesions, and radiation dosage more than 50 Gray (Gy)
- The pathophysiology of SMART syndrome is likely multifactorial and not well understood due to the rarity of the disease and the lack of histopathological findings in all the reported cases.

CNS Toxicity

- Acute late-onset encephalopathy after radiotherapy **(ALERT Syndrome)** is a disease entity related to post-irradiation inflammatory endothelial damage or post-radiation mitochondrial damage, as suggested by the similarity of clinical and MRI pattern presentation to stroke-like episodes occurring in inherited mitochondrial disorders
- Common features include a remote history of irradiation in young and middle age, acute but long-lasting (4–24 days) altered consciousness (Glasgow Coma Scale score 3–10), and clinical improvement after high-dose steroids, associated with multifocal and bilateral brain dysfunction on EEG and MRI.

CNS Toxicity

Radiation May Induce Secondary Brain Tumors

- A high risk for the development of CNS secondary malignancies was reported as a late radiation-induced brain injury.
- The pathogenic mechanism supposed is direct damage combined with abnormal DNA repair mechanisms related to the use of radiation therapy in combination with alkylating agents and etoposide and is more common in children than in adults
- Meningiomas and gliomas are secondary brain tumors due to radiation therapy, with a higher risk of radiation induced damage in younger children and those treated with higher doses of radiation

CNS Toxicity

- Radiation-induced vasculopathy can occur months to years later after radiation therapy due to head or neck cancer
- Focal small-vessel arteriopathy, moyamoya arteriopathy, internal carotid stenosis, and hemorrhage or infarction have been noted in survivors of brain tumors who received radiation therapy several years previously
- The risk factors for developing radiation vasculopathy include patients receiving adjunctive chemotherapy, radiotherapy at a young age, and a higher radiation dose or having other vascular risk factors
- In particular, the development of moyamoya syndrome (MMS) has been rarely reported in children receiving proton beam therapy for brain tumors several years after therapy
- The risk of developing MMS has been estimated to increase by 7% for every 100 cGy increase in radiation dose above 5000 cGy, with a delay in the occurrence of approx. 5-12 years

Moya Moya Syndrome

Moyamoya disease is a chronic and progressive condition of the arteries in the brain. People with moyamoya disease have narrowing of these blood vessels that leads to blockages and can eventually cause

- Ischemic stroke
- Hemorrhagic stroke
- Seizures.

Endocrine Toxicity [Pituitary]

- Impairment of Growth hormone occurs in 30% after 30Gy and 50% after 30-50 Gy dose to Pituitary
- Gonadotrophin deficiency occurs in 20-50% following a dose of 30-40Gy to Pituitary
- Premature activation of Hypothalamus- Pituitary-Gonadal axis resulting in precocious puberty after 30 Gy
- TSH and ACTH deficiency occur after >30Gy in 9% but significant increase after 50Gy
- Hyperprolactinemia due to a radiation induced reduction in the inhibitory neurotransmitter Dopamine in females receiving doses 40Gy

Endocrine Toxicity [Thyroid]

- Dose as small as 50-100mGy are associated with Thyroid Cancer
- Linear dose-response upto about 10-20 Gy
- Risk persists for atleast four decades after exposure
- Children are more vulnerable Because of

Growing Tissue

Mitosis

Excess risk of Mutation

Endocrine Toxicity [Gonads]

- Testes consist of spermatogonia and Leydig cells
- Spermatogonia are highly radiosensitive and permanent impairment of spermatogenesis after 2-3Gy
- Radiation Dose 4-7.5Gy leads to almost permanent sterility
- Leydig Cells produce Testosterone and can tolerate doses upto 12Gy
- Dose of >20Gy was associated with increased prevalence of need for Testosterone replacement

Endocrine Toxicity [Gonads]

- Doses >4-5Gy to ovaries and uterus are associated with subfertility
- Dose of 5Gy absorbed by Ovaries lead to premature menopause
- Doses of 1-10 Gy to Ovaries and uterus are associated with stillbirth and neonatal death
- Doses of >5Gy to Uterus and >0.5-2.5Gy to ovaries has been associated with preterm delievery. Low birth weight and small strature children
- Dose to ovaries and Uterus should be totally avoided or kept<5Gy
- Smoking and Chemotherapy increases the incidence of toxicity

Endocrine Toxicity [Pancreas]

- Dose of >10Gy to Pancreatic Tail is associated with risk of developing of DM
- This Dose effect is most pronounced in age group >2-10 years
- No Dose response relation was found in children >15 years of age
- The Pancreatic Tail should be delineated as an organ at risk for children<10years and dose limited to<10Gy
- Stricter constraints for young children <2Gy

Endocrine Toxicity [Liver]

- The data for dose constraints for children is very limited
- Late radiation induced toxicity such as Cirrhosis, fibrosis are uncommon in long term
- Mean liver doses advised are<13-20 Gy or <15Gy to >700ml of normal Liver

Effects on Growth

- Vertebrae are in the period of accelerated Growth <6 years of age and at puberty
- Doses more than >20Gy to spinal column leads to complications
- Mild Scoliosis at >30Gy and Severe Scoliosis at >37 Gy
- Bone and Muscle Hypoplasia at >28-30Gy
- Permanent growth retardation is seen after >12Gy to appendicular skeleton and epiphyseal plate
- Radiation to epiphyseal plate in males <14 years and females <12 years leads to premature closure of epiphyseal plate

Effects On Vision

- Dose to lens >2Gy injures the fibres
- Dose <6.5Gy there is 33% risk of progression to cataract over a period of 8 years
- Dose 6.5 to 11.5Gy lead to cataract over 4 years
- Dose constraint of 5-10 Gy is for adults and also for childhood
- Radiation retinopathy occurs over a dose of 45Gy
- Lacrimal Gland injury occurs at >57 Gy with permanent loss of tears
- Dry Eye Syndrome occurs with Dose >40 Gy to Cornea and Conjunctiva

Effect on Hearing

- Average volume of Cochlea is 0.60 ml
- A Dose Volume is not feasible
- In children sensorineural hearing loss occurs and is reported at dose >40 Gy
- Concomittant cisplatin has additive effect

Second Malignancy

- Thyroid Adenoma <18Gy
- Thyroid Carcinoma <30 Gy
- Chondrosarcoma >30 Gy
- Sarcoma >60Gy
- Skin
- Brain
- Breast After RT for Hodgkin to Mediastinum

Effect on Foetus

- Developing Foetus most sensitive during first 14 days
- Significant Consequential damage during organogenesis period 2-8 weeks
- Less than 0.05Gy has no effect
- Deterministic effect if dose more than 0.05Gy
- Radiation Induced Sequelae

Growth Retardation

Congenital Malformations

Ocular Abnormalities

Intellectual Disability

Dose Constraints Paediatrics

High dose-volume constraints: A systematic comparison of US and European pediatric cancer treatment protocols.

	constraints		constraints	
	D_{max}	Volumetric constraint	D_{max}	Volume constra
Bladder		V70 < 20%	<60	
Brain	<60		<60	
Brainstem		V63 < 10%		V64 < 1
Cornea-lacrimal	<41.4		<41.4	
Heart	<50		<30.6	
Kidneys	<20		<19.8	
Lungs		V20< 20%	<18	
Liver	<50		<23.4	
Mandible		V77 < 1cc	<60	
Optic chiasm	<60		<60	
Optic nerves	<60		<60	
Bowel	<50		<50	
Spinal cord		V57<10%	<54	

Take Home Message

- Radiation Toxicity is difficult to treat
- Always stick to Dose Constraints
- Plan Cautiously and Meticulously
- Children have long life expectancy
- Morbidity due to treatment side effects is unacceptable


SRI GURU RAM DAS UNIVERSITY
OF HEALTH SCIENCES, SRI AMRITSAR


THANK
YOU!