Radiation induced CNS toxicity

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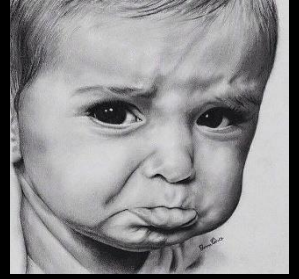
ICRO Bhopal, 20.4.24

INTRODUCTION

- ✓ Radiation therapy is an integral part of treatment for primary and secondary malignant CNS neoplasms
- ✓ Prevalence of late radiation induced brain injury
  - ✓ Based on clinical and imaging features: 37 - 58% among survivors, (overall prevalence of 14%)
  - ✓ Based on histologic features: 4 - 5%
- ✓ Early recognition of treatment-associated neurologic adverse effects is essential
- ✓ It may require alteration of the overall cancer treatment plan to avoid more severe or potentially permanent neural injury.
- ✓ Severity of symptoms perceived by a patient and the objective findings on patient examination and imaging evaluation do not always correlate (eg, cognitive symptoms may not be associated with abnormal imaging findings).
- ✓ Conversely, abnormal imaging findings (eg, presence of diffuse leukoencephalopathy) do not always produce symptoms or detectable neurologic deficits.
- ✓ Some neuroprotective strategies (eg, hippocampal-sparing radiation therapy and early use of neuro-stimulants) may mitigate cancer therapy–induced neurotoxicity and are increasingly incorporated in patient management with the goal of improving neurocognition and quality of life.



2/3 rd survivors have at least one debilitating problem

- Retardation of cognitive function
- Impairment of social adjustment
- Poor QOL
- Neuroendocrine disorders
- Second cancers
- **Adverse effects of RT**
- Growth impairment
- Vascular disorder
- Endocrine dysfunction
- Musculoskeletal hypoplasia
- Acoustic disturbance

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I am marooned in a sea of emotions and so will u as my talk progresses.

SIDE EFFECTS ASSOCIATED WITH DAMAGE TO HEALTHY BRAIN TISSUE

Hippocampal-related learning and memory dysfunction

Cognitive domains-learning, processing speed, memory, executive function, and attention.

Focal neurological deficits

Increased intracranial pressure

Secondary epilepsy

Progressive dementia

Peripheral neuropathy

Encephalopathy, Leukoencephalopathy

Brain atrophy

Neurovascular syndromes

Development of secondary nervous system tumors

Acute CNS syndrome is seen with > 30 Gy; white matter necrosis is seen with > 60 Gy

Despite the advent of modern RT techniques, radiation-induced brain injury remains an important complication where cognitive impairment can range from mild to severe and more rarely progressive and debilitating.

CLASSIFICATION OF RT-INDUCED BRAIN INJURY

1. **Acute**

- Transient
- Within days to weeks after RT
- Due to effect of RT on oligodendrogial cells or myelin producing cells , BBB disruption, neuro-inflammation, edema

- Relieved with steroids
- Edema
- Headache
- Drowsiness
- Irritability
- Mental state alteration

2. **Early delayed**

- Transient
- 1-6 months after RT
- Transient demyelination

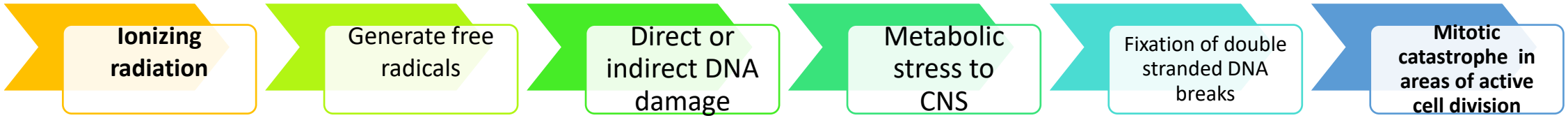
- Somnolence
- Attention deficits
- Short-term memory loss
- Fatigue
- Nausea

3. **Late delayed**

- 6 months after RT
- Delayed and progressive

- Due to direct tissue or endothelial damage
- White matter necrosis
- Leukoencephalopathy
- Vascular abnormalities
- Permanent demyelination gliosis
- Lasting cognitive impairment
- Partial loss of power and dyskinesia
- Endocrinopathy
- Secondary tumors

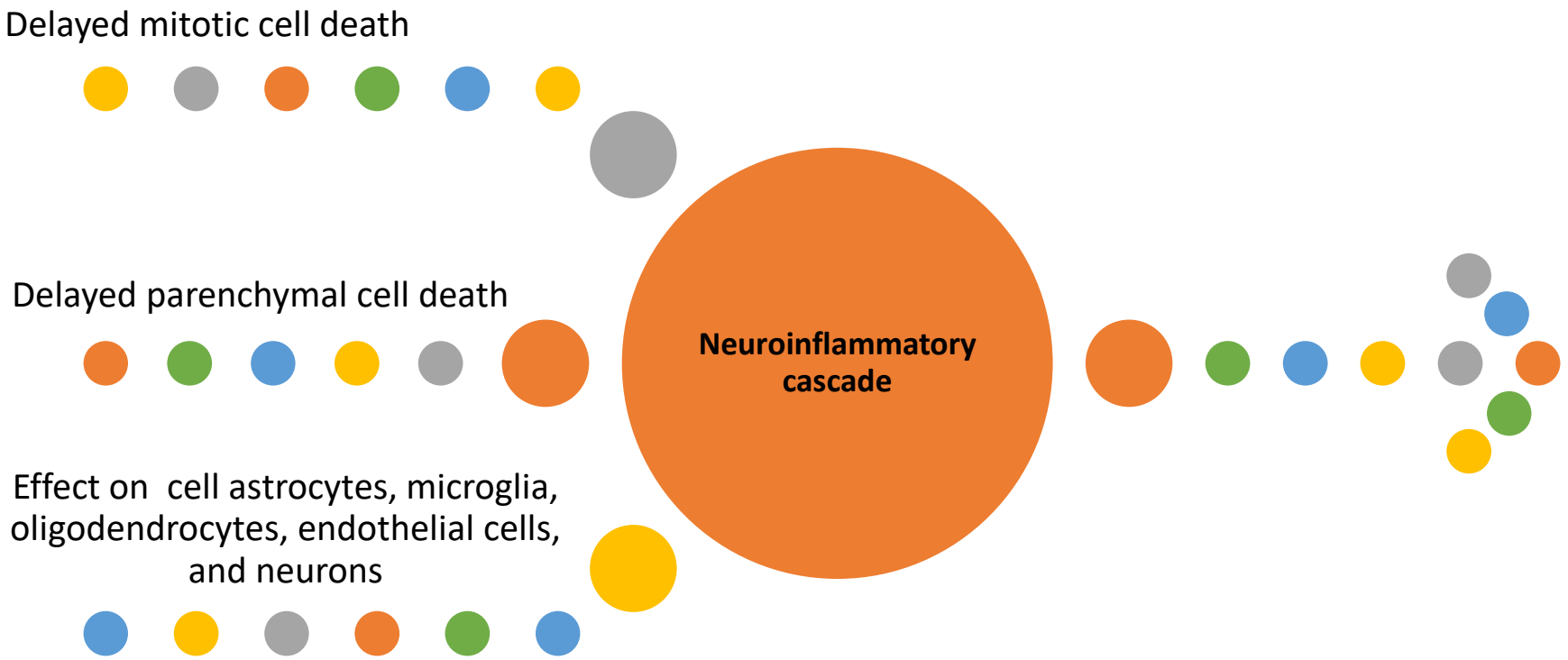
MECHANISM OF RT INDUCED TOXICITY



Normal mature CNS (mitotic potential is limited), other mechanisms of radiation-induced damage: oxidation of the lipid bilayer, changes in microvascular permeability, cell-cell junctional complex rearrangements, mitochondrial alterations inducing additional oxidative stress

RT →DNA damage + subcellular alterations= altered tumor microenvironment, cellular architecture, permeability of tumor vasculature and permeation of drugs within the CNS

MECHANISM OF RT INDUCED BRAIN INJURY



- ✓ Damage to blood brain barrier
- ✓ Neural progenitor cell death
- ✓ Hippocampus damage
- ✓ Direct activation of glia
- ✓ Senescence associated secretory phenotype (SASP)

Challenges in determining the precise frequency of cognitive decline

May be under estimated due to a number of factors including

(1) long-term FU is required to detect late post treatment changes

(2) Attrition bias favoring those with higher cognitive functioning

and not counting those with lower cognitive functioning

(3) Paucity of clinical studies examining histological confirmed

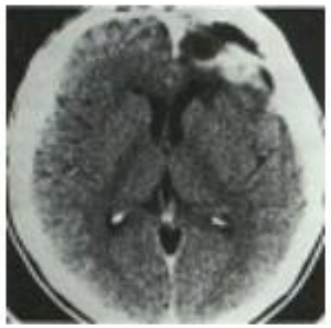
RT-induced injury.

FACTORS AFFECTING NEUROTOXICITY

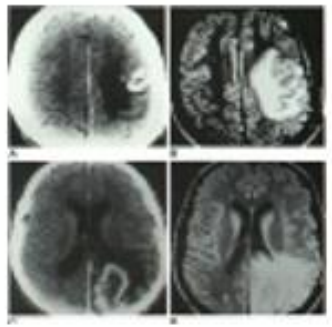
- ✓ Variability in time to assessment
- ✓ Definition of neurocognitive impairment
- ✓ Tumor type
- ✓ Patient age
- ✓ Medical comorbidities
- ✓ Steroids and antiepileptics
- ✓ Psychological and genetic predispositions
- ✓ Underlying malignancy
- ✓ Baseline neurocognitive function
- ✓ Disease progression
- ✓ Genetic susceptibility
- ✓ Radiotherapy modality-(WBRT, PBRT, stereotactic)
- ✓ Radiotherapy technology- Photons, protons, carbon ions
- ✓ Radiation dose and fractionation
- ✓ Differential radiosensitivity between sub-compartments of brain
- ✓ Multimodal treatments including concurrent chemotherapy, surgery

Table 2. Factors associated with radiation tolerance of the normal central nervous system tissues

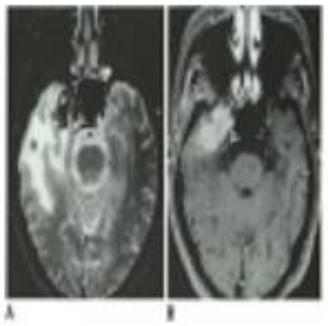
Factor*	Factors for increased risk of injury	Tolerance increased by
Total dose	Higher total dose	Decreasing total dose, hyperfractionation‡, radiosensitizers
Dose per fraction	Dose per fraction >180–200 cGy	Decreasing dose/fraction to ≤ 180–200 cGy
Volume	Increased volume, e.g., whole-organ radiation	Decreasing volume, e.g., partial-organ radiation
Host factors	Medical illness, e.g., hypertension, diabetes	Unknown, possibly radioprotectors
Beam quality	High LET radiation beams, e.g., neutrons	Low LET beams, e.g., photons
Adjunctive therapy	Concomitant use of CNS toxic drugs, e.g., methotrexate	Avoid concomitant use of CNS toxic



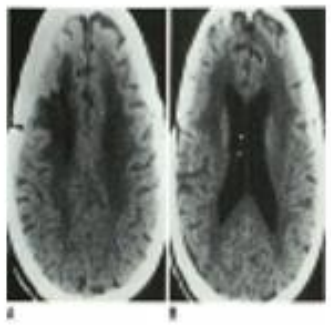
Focal radiation necrosis



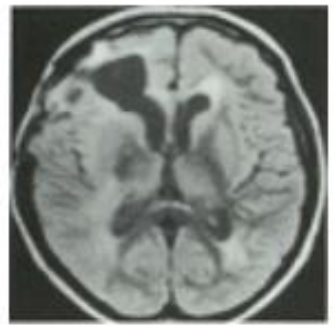
Differential diagnoses



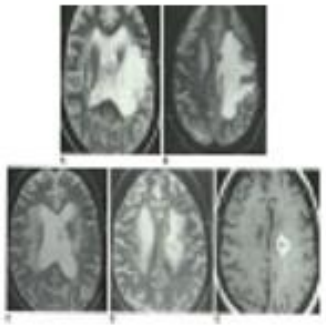
Hemorrhagic radiation injury



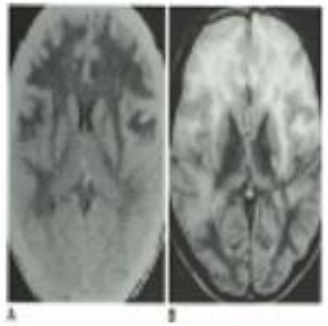
Diffuse white matter injury



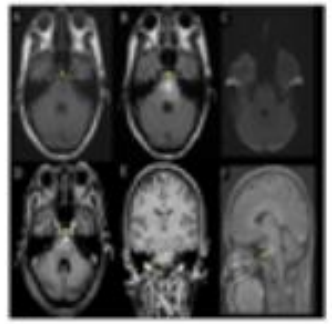
Diffuse white matter change (severe)

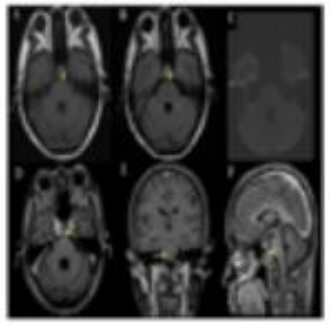


Concurrent focal and diffuse white matter injury

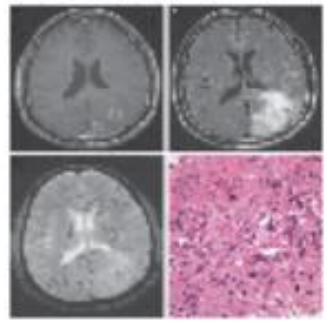


Diffuse necrotizing leukoencephalopathy

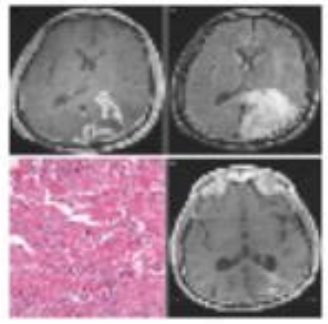




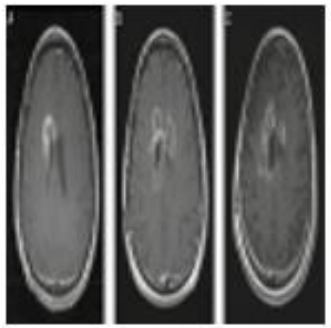
Radiation necrosis of pons



Abnormal enhancement in left occipital lobe



Irregular enhancement around surgical cavity



Pseudoprogression

Management of early reactions

Fatigue	Lack of improvement by rest Methylphenidate 10 mg BD , escalate to 30 mg BD in 1-2 week increments , dose limiting toxicity- anxiety and insomnia
Skin erythema	Anti-inflammatory, moisturising creams , 1 % hydrocortisone BD, Moist desquamation behind ears or in ECA needs skin creams or corticosporin otic suspension
Hair loss	Scalp sparing radiation, partial brain or focal radiation, SRS Keep scalp dose < 40 Gy

OPTIC NEUROTOXICITY

Retina
Dmax <45-50Gy

Cornea
D0.03 cc , 50 Gy

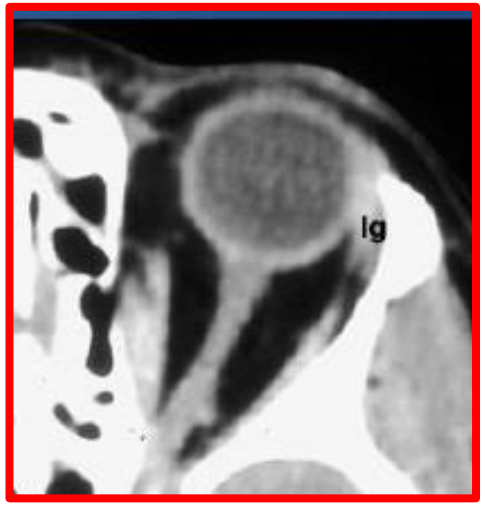
Lens
2 Gy- cataract
<6.5 Gy- 33% risk of progressive cataract at 8 years,
6.5 and 11.5 Gy- 66% risk of cataract progression at 4 years
Adults- Dmax 5-10Gy

Lacrimal gland
Dmean < 25 Gy
>40 Gy to lacrimal gland –dry eye
>57 Gy-permanent loss of tear secretion
100% rate of atrophy & fibrosis
Try to keep V30 less than 50%

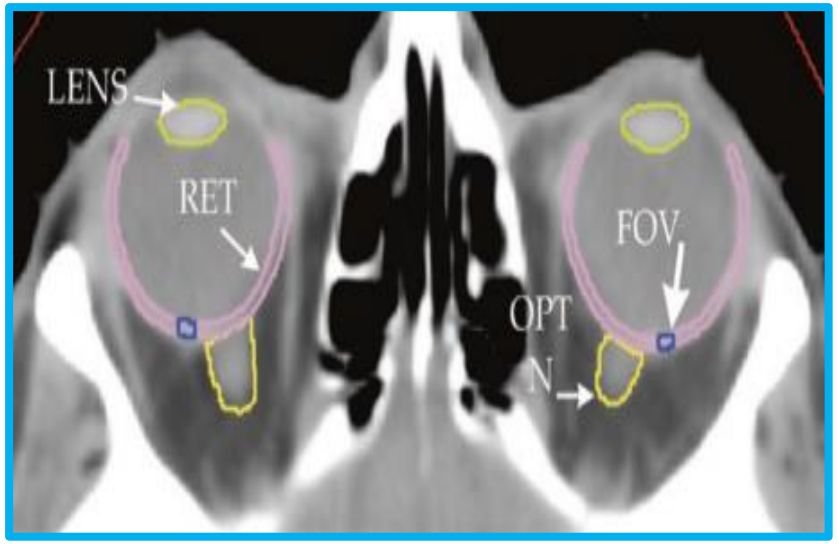
Oral cavity- Dmean <40 Gy, < 1cc > 70 Gy

Risk of cataract
20% with lens doses of 7 Gy
>70% with doses >20 Gy

FSRS- RION risk
1% NTCP risks
10 Gy/ 1F, 20 Gy/ 3 F, and 25 Gy/ 5 F
AAPM TG101 report
D 0.035 cc or less <10 Gy/1F, 17.4 Gy/3F, and 25 Gy/5F
D0.2 cc < 8 Gy/1F, 15.3 Gy/3F & 23 Gy/ 5F



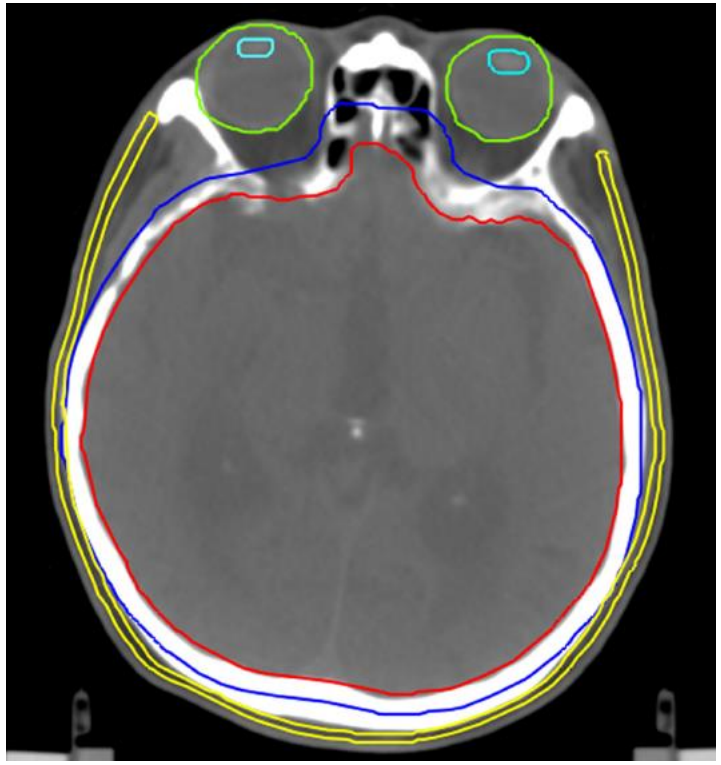
Caivano 2015Ann Palliat Med ;4(1):35-38



Though fovea size is relatively small compared to the rest of the retina, it is the only area of the retina where 20/20 vision is attainable and it is critical for seeing fine detail and colour.
It is employed for accurate vision in the direction where it is pointed. It comprises less than 1% of retinal size but takes up over 50% of the visual cortex

Scoccianti et al. / Radiotherapy and Oncology 114 (2015) 230–238, Arain 2015

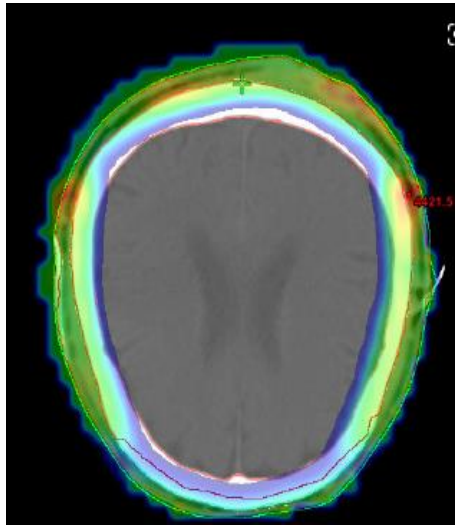
Scalp hair loss



Risk of permanent or severe hair loss increases with doses >40 Gy

WBRT 30 Gy/10 F – mean scalp dose 16–18 Gy
short period of temporary alopecia
Persistent alopecia – Dmax 36.1 Gy ,Grade 2 alopecia 50%
The dose is comparable to 30 Gy in 10 fractions if α/β ratio is 3 Gy for late toxicity

The scalp was defined as the region at a depth from 3 to 5 mm below the skin surface



Total scalp RT used in
Lymphoma
Angiosarcoma
Mycosis fungoides
Basal cell ca.
squamous cell

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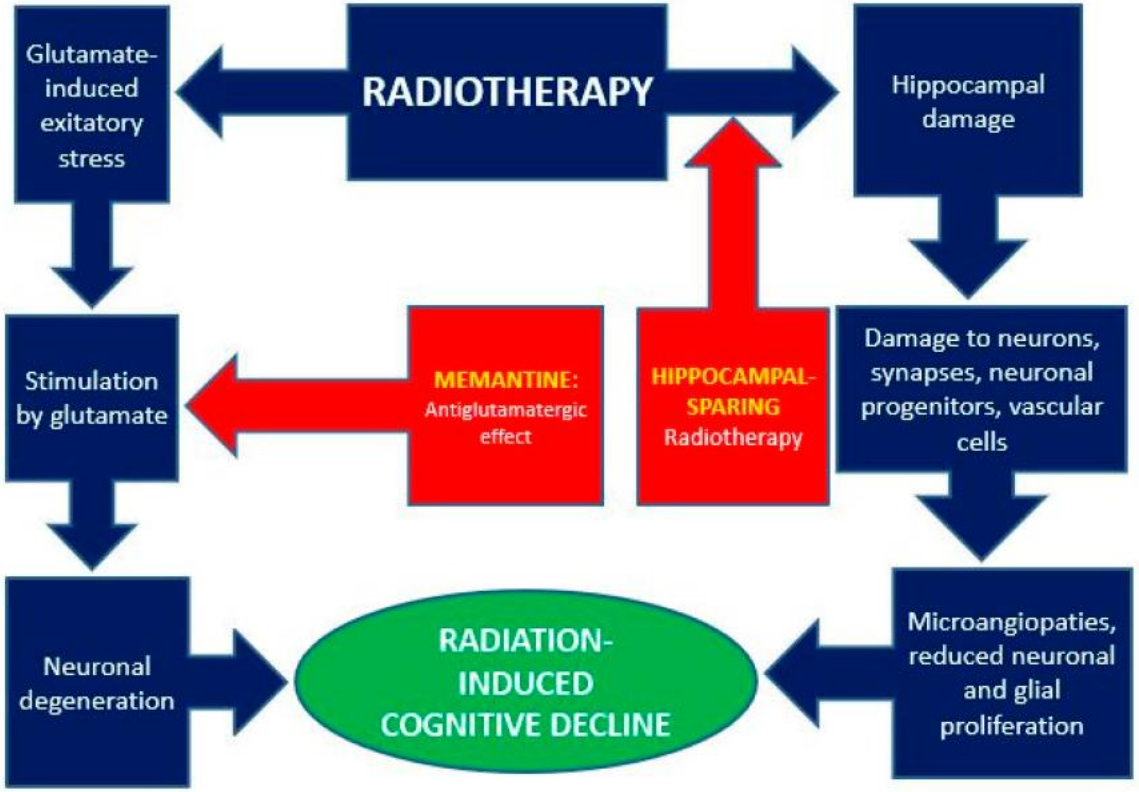
Shirata 2020

Radiation-induced Cognitive dysfunction

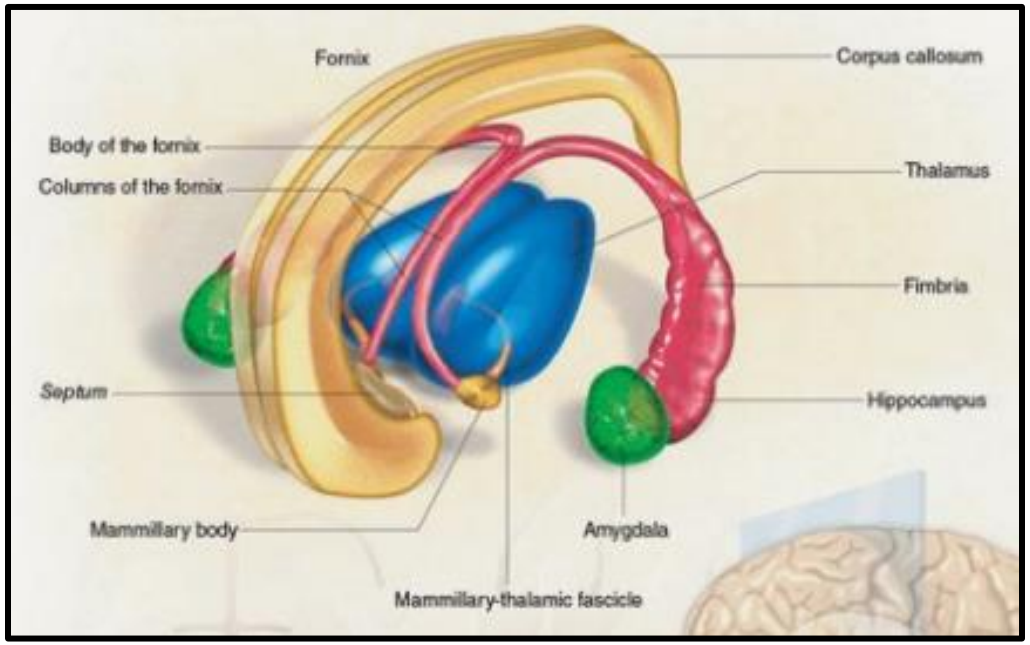


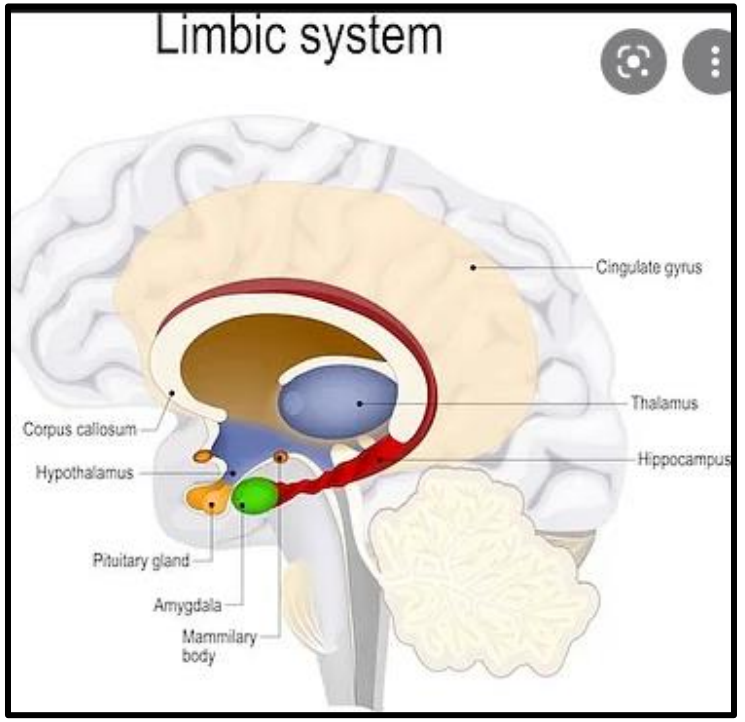
- Diagnosed in approx 90% pts. post RT, can evolve into dementia in 2–5%
- Presents with- memory loss, an impaired ability to plan activities and behavioral changes

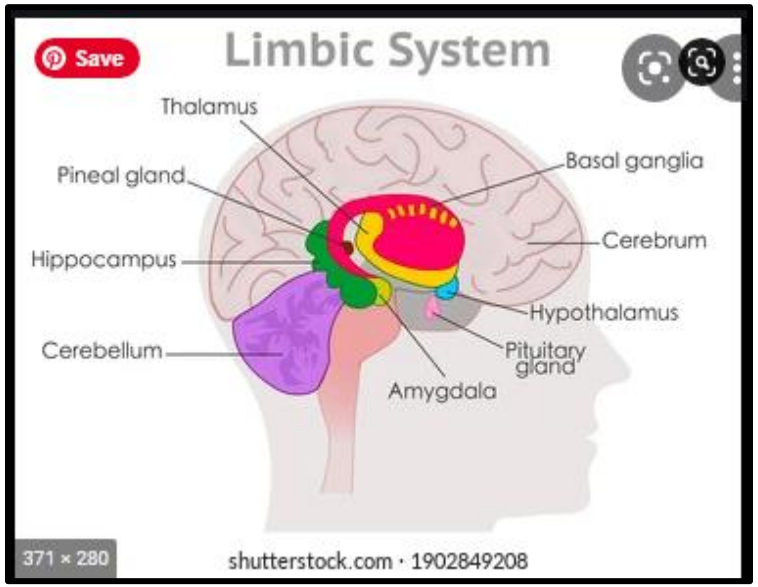
- **Risk factors for the development of CD**
- Age (<7 years, >60 years)
- Large irradiation volume
- High dose per fraction
- Chemotherapy
- Impaired pre-irradiation functional status
- Vascular damage from hypertension and/or diabetes
- Worsened by- tu. Progression, antiepileptic drugs, paraneoplastic syndromes & corticosteroids

Sampoli 2022 Cancers **2022**, 14, 2736.

Limbic system







Hippocampus -belongs to limbic system.
Located in medial temporal lobe
Seahorse shaped
Very important role in consolidating information in short-term & long-term memory and spatial navigation.

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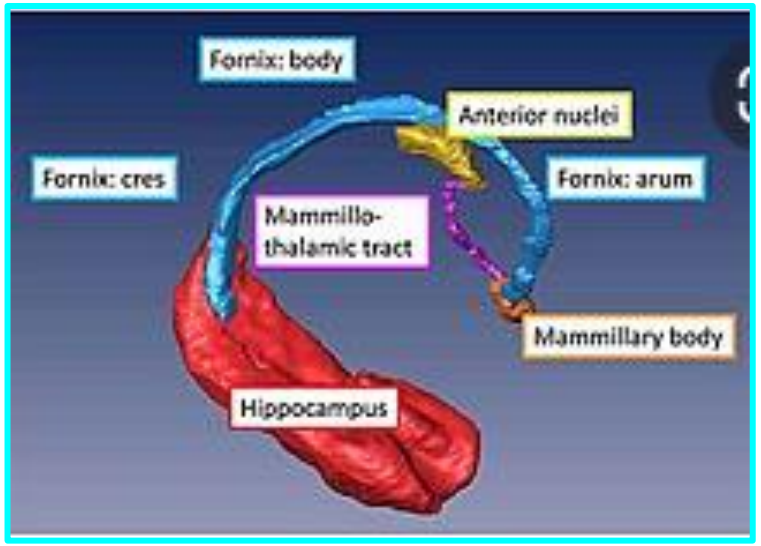

FORNIX

- ✓ T1 weighted MRI
- ✓ Main output tract of the hippocampus
- ✓ Essential for memory consolidation
- ✓ C-shaped structure
- ✓ 2 symmetrical arch-like bundles of white matter
- ✓ Connects hippocampi infero-post to the mammillary bodies ant.
- ✓ After leaving the hippocampi, run initially medial to the temporal horn of the lateral ventricle.
- ✓ Then, arch antero-sup underneath the corpus callosum.
- ✓ Unite under the septum pellucidum
- ✓ Finally diverge anteriorly, curving behind the anterior commissure and in front of the inter-ventricular foramen of Monro).
- ✓ The contour stops at the cranial border of the mammillary bodies

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Hippocampus

Periventricular and peri-granular zones of hippocampus sites for neurogenesis

A) Parahippocampal gyrus

B) Temporal horn

C)Ambient cistern

D)Fimbriae

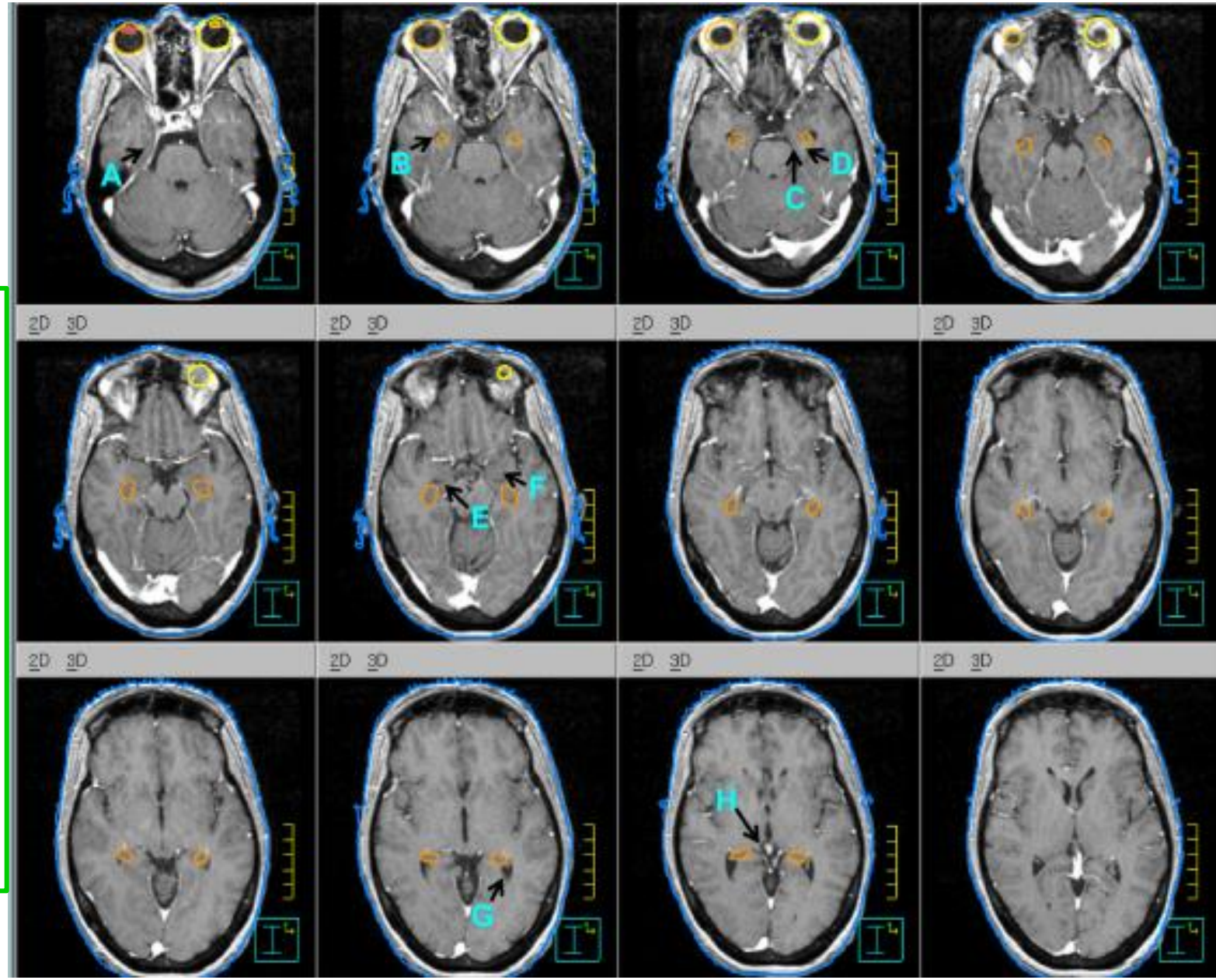
E) Uncal recess

F)Amygdala

G)Atrium of the lateral ventricle

H) Lateral edges of the quadrageminal cisterns

The historical control demonstrated a 30% mean relative decline in cognitive function from baseline in 4 months, while hippocampal avoidance resulted in a 7% mean relative decline in cognitive function.



Hippocampus WBRT
Max Dose: 16 Gy; D100% < 9 GY

T1 sequence , Hippocampal avoidance volume is 2 % of brain volume

Int J Radiat Oncol Biol Phys. 2010 November 15; 78(4): 1244–1252

Hippocampus

Jalali et al- Age <13yrs =>10% drop in the VQ subdomain (P = 0.02).
Mean left hippocampus dose >25 Gy =>10% drop in the PQ subdomain (P = 0.03)

Mean left hippocampus dose of >30.7 Gy- >10% decline in FSIQ at 3 years
13% volume of left temporal lobe receiving >43.2 Gy - FSIQ impairment

RTOG 0933 study- hippocampal-sparing WBRT (D100 of <9Gy; Dmax of 16 Gy)
EQD2 values < 12.60 Gy, <8.81 Gy, <7.45 Gy, and <5.83 Gy to 0%, 10%, 50%, and 80% volume associated with preserved verbal memory.

Gondi et al ->7.3 Gy to 40% volume of bilateral hippocampi - delayed memory recall in LGG

St. Jude-Vol. of B/L hippocampus receiving >40 Gy- decline in total memory recall

Seibert et al- Hippocampus volume loss is 0.13% per Gy of mean dose(GBM 4mm3 lost per Gy) - significant one year after high-dose RT(> 40 Gy), but not after low-dose radiotherapy (<10 Gy)

Ma et al/ Okoukoni –**V55 Gy** impaired Hopkins Verbal Learning Test-Revised Delayed Recall

✓D100% hippocampus doses >10.9 Gy-20% probability of decline
59.3 Gy- 50% probability

Hydrocephalus - affect measures of various domains of NCF via increased intracranial pressure stretching and distorting various neural pathways

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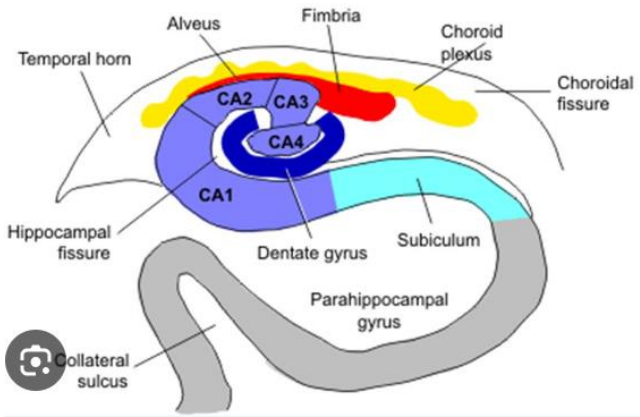
Dentate gyrus and cornu ammonus of the hippocampal region- neurons in the sub-granular zone niche for the neural progenitor cells



Memantine 5 mg BD , titrate at 5 mg/ week then 10 mg BD x 6 months post RT

Connor 2021Cancer J; 27(5): 353–363, Goda 2020 neuro-Oncol.

Neurocognition and mean radiotherapy dose to vulnerable brain structures: new organs at risk?

Hippocampus- correlated with lower performance on processing speed and working memory.
Cochleae –hearing loss associated with intellectual impairment and lower academic performance
Optic chiasm/nerve -optic neuropathy can impact neurocognition through connections to the CNS
Cerebellum complex interaction with the cerebral cortex through the cerebro-cerebellar loops (the corticoponto-cerebellar pathway and cerebello-thalamo-cortical pathway) important role in sensorimotor function and neurocognition such as working memory, language, and executive function
Vermis several connectional networks to the brain such as pons, hippocampus and limbic structures. Associated with neurocognitive decline and social-emotional behavioral problems
Thalamus-a widespread broader cortico-subcortical network, injuries lead to late effects with visual attention and memory
Hypothalamic-pituitary (HP) Lower performance on IQ and memory

Higher dose to cochleae, optic nerve, cerebellum, vermis and pons -lower performance on particularly full-scale IQ (FIQ), Perceptual Reasoning (PRI), Working Memory (WMI) and Processing Speed Index (PSI)
Hippocampus- lower performance on processing speed and working memory.
WBRT- pituitary gland- working memory affected

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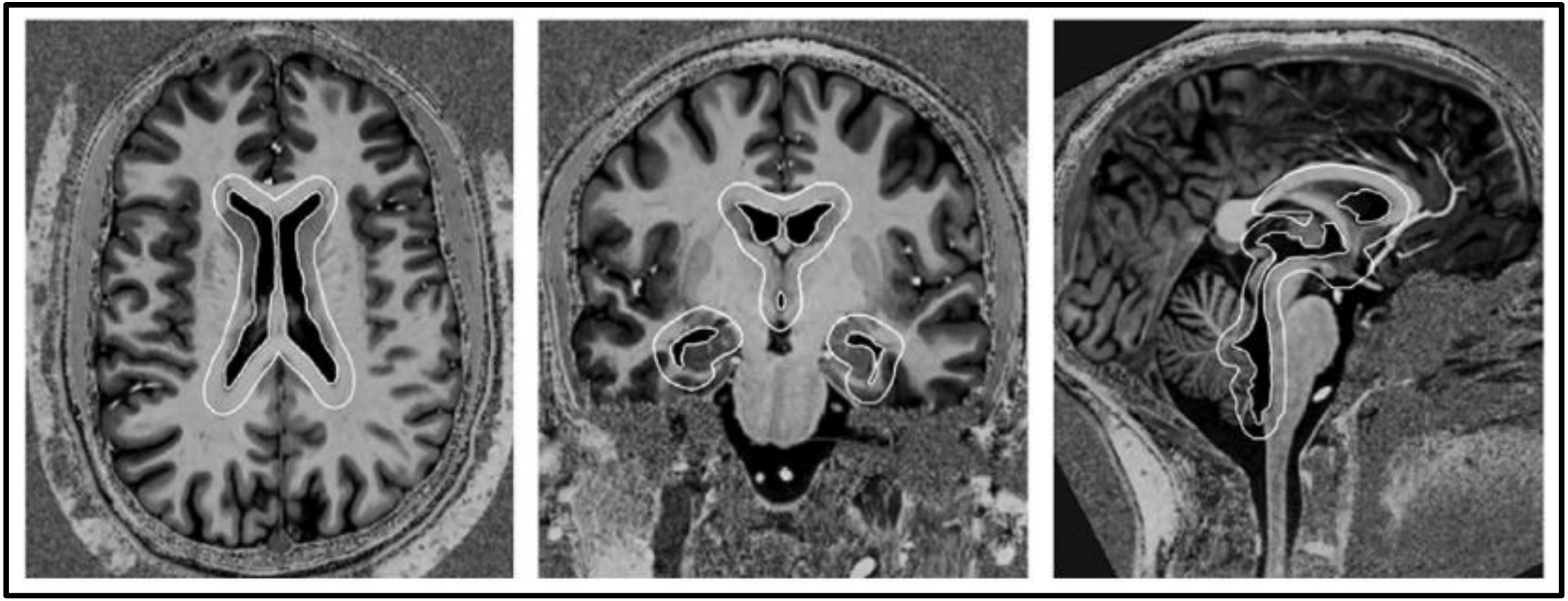
Söderström et al. Radiation Oncology (2023) 18:132

PERIVENTRICULAR SPACE



The innermost region of the PVS, known as subventricular zone, constitutes a major neural stem cells niche and is associated with gliomagenesis

The two lateral ventricles, including their different parts: frontal horn, central parietal part, occipital horn, and temporal horn

The third ventricle, including the supraoptic recess, the infundibular recess, and the suprapineal recess

The fourth ventricle,2 Foramina of Monro, the Sylvian aqueduct, and 2 foramina of Luschka

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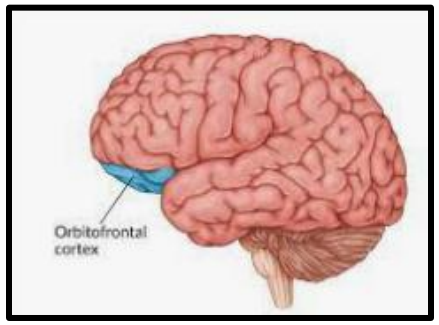
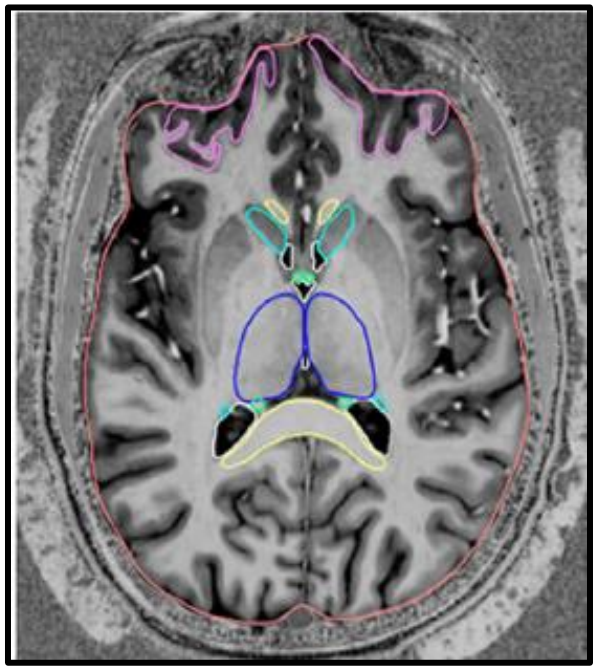
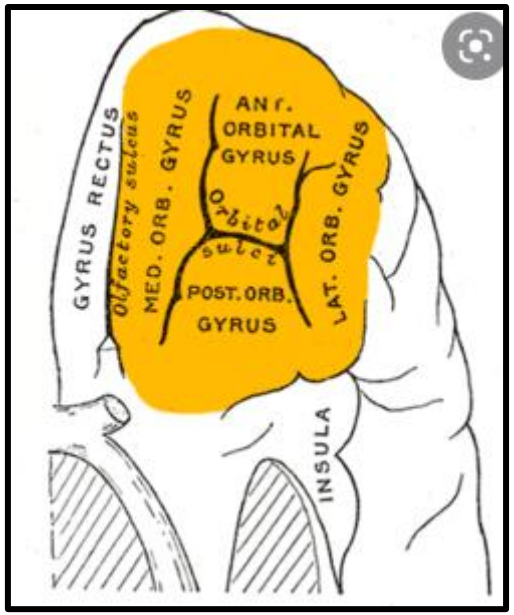


Orbito-frontal cortex



- ✓Cortex located at the ventral side of the frontal lobe.
- ✓Role in memory, emotional functioning and cognition, in particular reward-based decision making
- ✓T1-weighted MRI is required for delineation
- ✓Easier to identify in the coronal plane, halfway through the frontal lobe (3–4 cm from the frontal pole of the brain)
- ✓At this level, the orbitofrontal cortex runs between the olfactory sulcus medially, and the lateral orbital sulcus laterally



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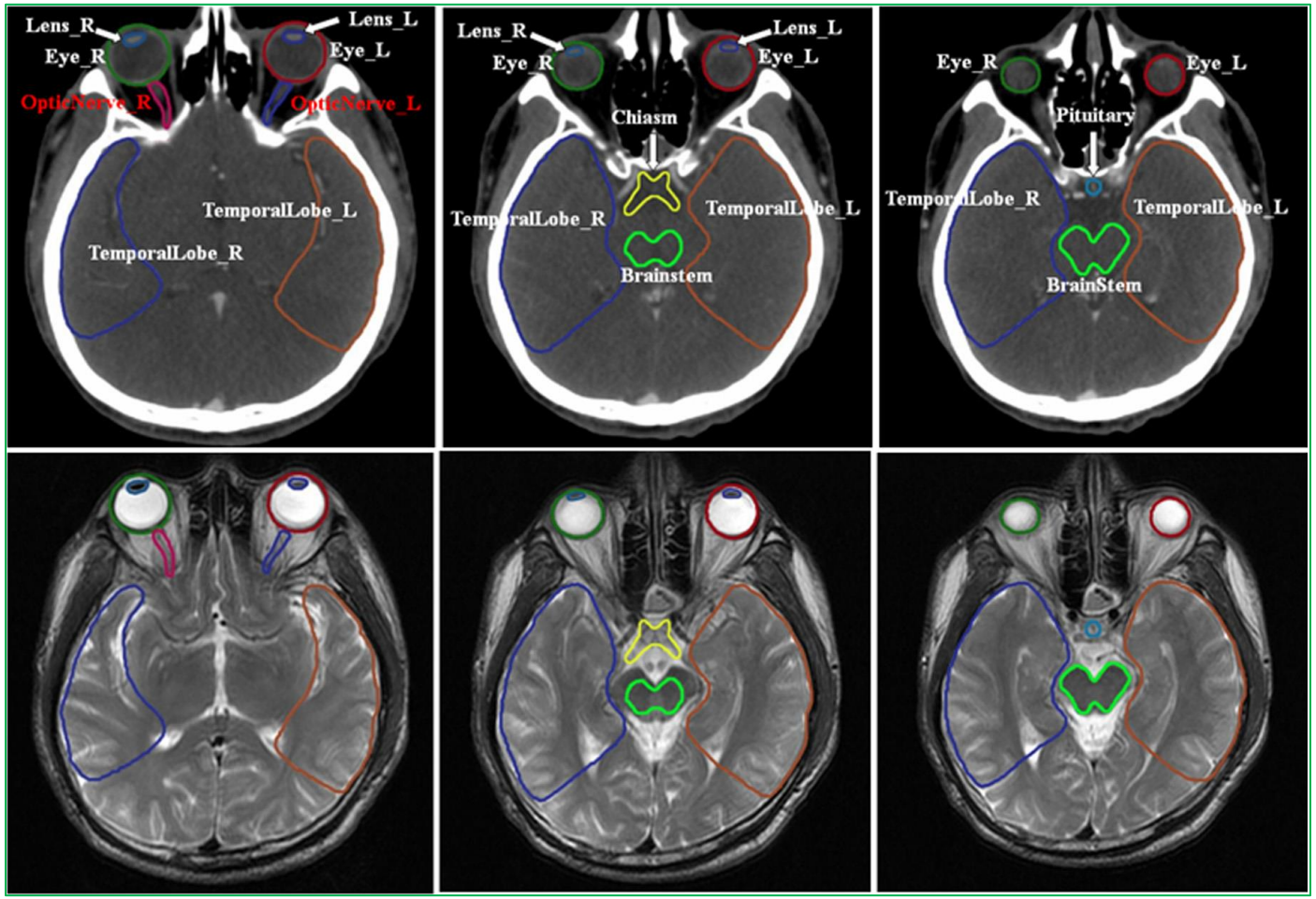
TEMPORAL LOBES

Organ	Standard TPS name [20]	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Temporal lobe	TemporalLobe*	Cranial edge of the sylvian fissure	Base of middle cranial fossa	Temporal bone and sylvian fissure, greater wing of sphenoid	Petrous part of temporal lobe, tentorium of cerebellum, incisura preoccipitalis	Temporal bone	Cavernous sinus, sphenoid sinus, sella turcica, and sylvian fissure including parahippocampal gyrus and hippocampus



- White matter of inferior temporal lobe & lower part of brain stem in nasopharyngeal carcinomas
- Based on site, RT induced brain injuries are classified as
  - Cerebral type
  - Brain stem type
  - Cerebellar type
  - Mixed type

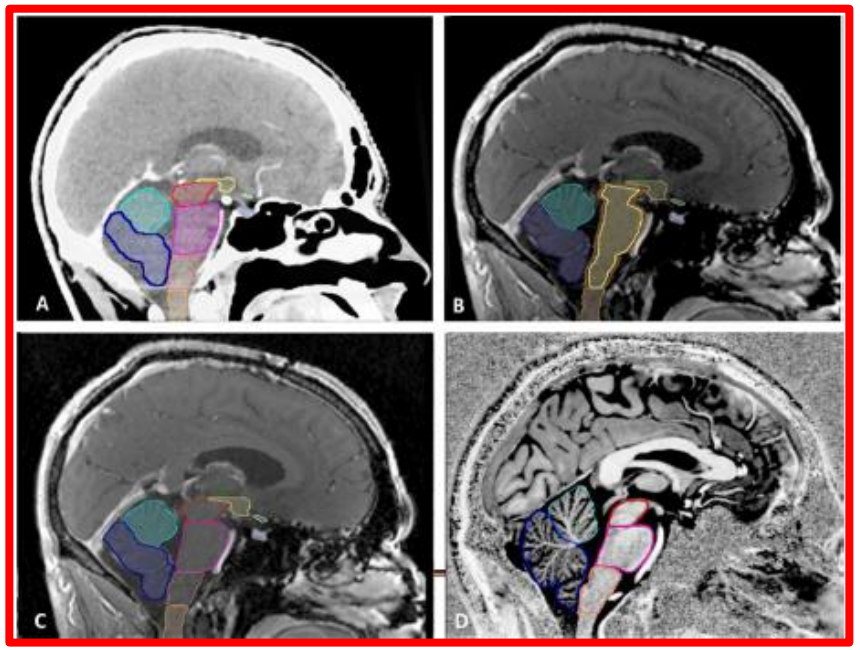
13% volume of left temporal lobe receiving >43.2 Gy - FSIQ impairment

Soccianti, Radiotherapy and Oncology 110 (2014) 390–397

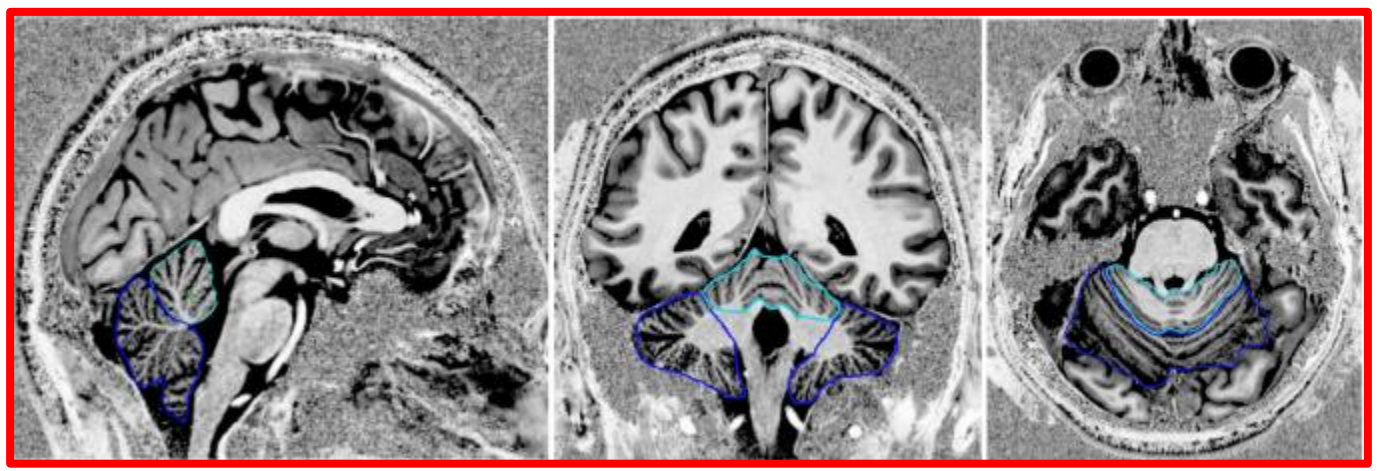
Editorial

The posterior cerebellum, a new organ at risk?

The cerebellum consists of two hemispheres divided by the vermis. These are organized into ten lobules
3 anterior-posterior divisions
: the primary fissure separates the anterior lobe (lobules I–V) from the posterior lobe (lobules VI–IX)
the posterolateral fissure separates the posterior lobe from the flocculonodular lobe (lobule X).



Merchant et al-
maximum dose **of < 36 Gy on the cerebellum**

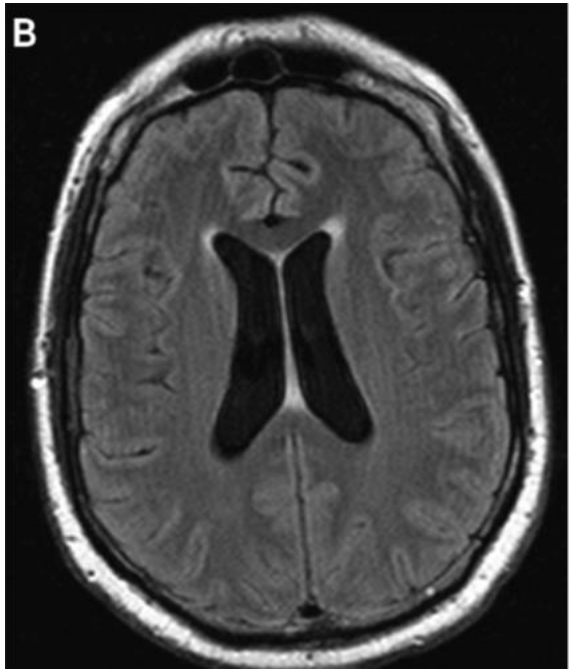


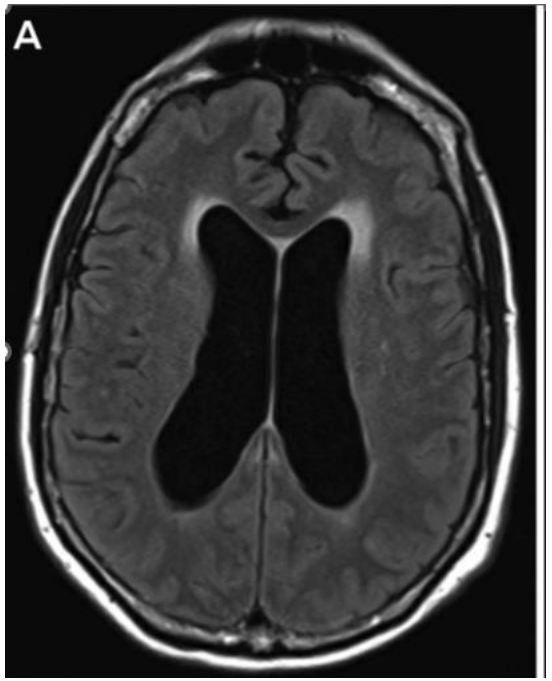
Indu Bansal, NH, Gurugram

Radiotherapy and Oncology 128 (2018) 37–43

LEUKOENCEPHALOPATHY

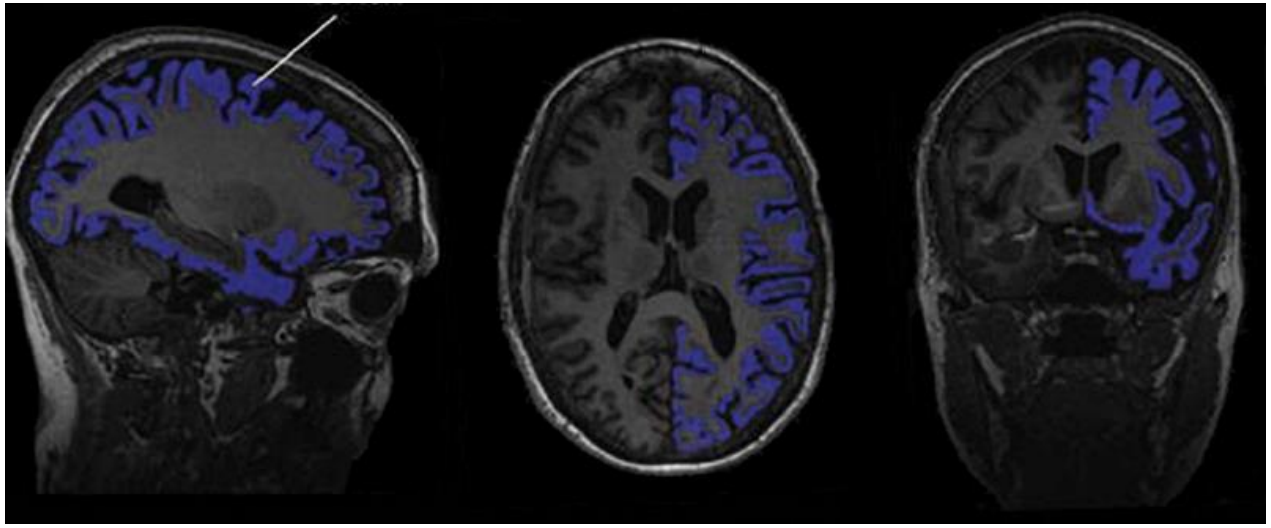
- Demyelination is a delayed RT-induced brain injury.
- Incidence - 5% to 30% after brain RT, higher with concurrent CT
- **Brain MRI** - increased T2/FLAIR signal intensity within the periventricular and deep white matter, which typically evolves months to years after treatment.
- Can be associated with brain volume loss and ventriculomegaly
- **Histopathologic findings** are demyelination, spongiform vacuolization, and gliosis
- **Symptoms**- Gait difficulties with frequent falls, cognitive impairment, and incontinence
- Resemble symptoms of normal pressure hydrocephalus.
- **Treatment**- VP shunting can be tried, although motor function is more likely to improve than autonomic or cognitive function

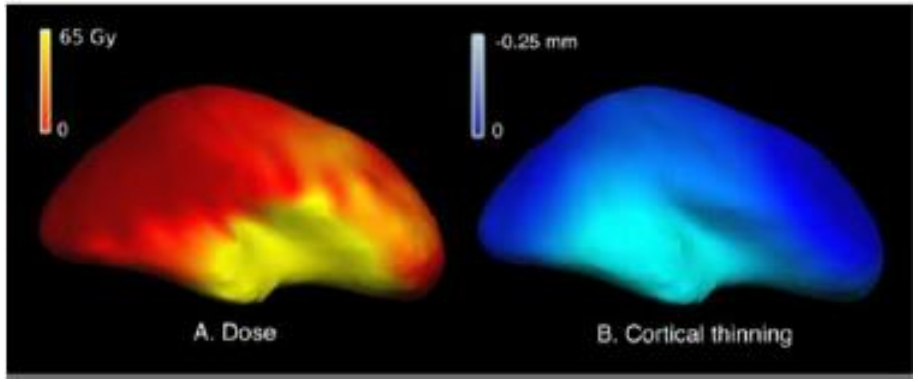




Dietrich 2018

Is cortical thinning post RT lobe dependent ?





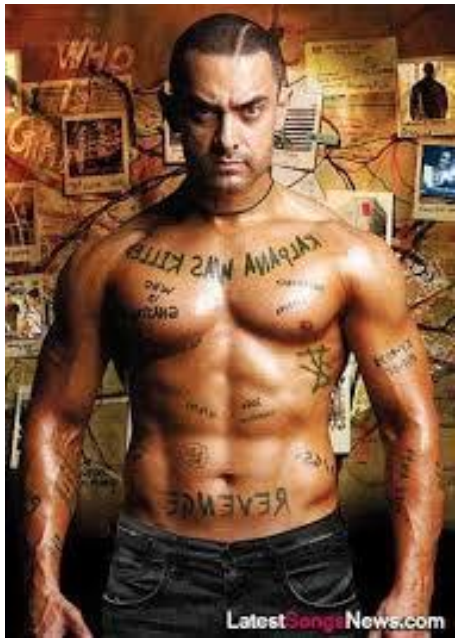
- Karunamuni – global cortical thickness decrease of 0.0033 mm/Gy with a breakpoint dose of 34.6 Gy above which regression slope was steeper
- **Temporal and limbic lobes most sensitive**
- Higher order cortical regions as (entorhinal, inf. parietal, reflecting memory and attention had more dose dependent thinning whereas primary cortical regions (Pericalcrine and paracentral) representing visual and motor function did not.

Connor Cancer J. 2021 ; 27(5): 353–363.

NEUROCOGNITIVE EFFECTS OF RT

- CNS tumor survivors were 10.8 fold less likely to be employed
- 16.2 fold more likely to be mentally incompetent
- 28.8 fold less likely to be able to drive a car

- Adult survivors had verbal and nonverbal global cognitive abilities 1 SD below normal
- **Mean decline in IQ of 12-14 points after RT**
- If age < 4 yrs decline in IQ 14 points
- **Reduction of CSI dose from 36 Gy to 23.4 Gy still leads to decline of 4.3 points /yr**
- Leads to deficits in attention/ working memory & processing speed



Impact of protons

- ✓ CSI with protons followed by post fossa boost lead to decline by 1.5 points/yr
- ✓ **Processing speed and verbal comprehension was reduced but perception reasoning and working memory were intact**.
- ✓ Protons reduce low dose and intermediate dose RT to brain leading to preservation of more white matter tracts and hence preserve memory.

- **Jalali et al , dose > 43.2 Gy to 13% of left temporal lobe associated with lower IQ.**
- Kahallay et al- improvement of 0.4 IQ points per year or 2 IQ points/yr at 5 yrs post RT with IMPT over IMRT.
- **Net IQ benefit of IMPT over IMRT is same regardless of which brain substructure is modelled with a median value of 2.6- 2.9 IQ points for 54 Gy (59.4Gy)**

Gross 2019

Vasculopathic effects

>50 Gy to the pre-pontine cistern had a 17.8-fold higher hazard ratio of death

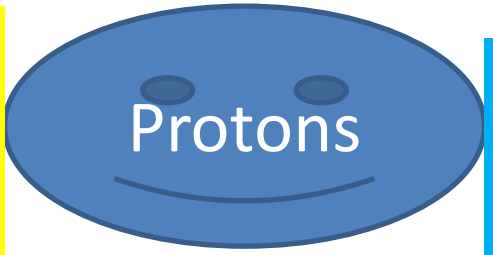
Cerebrovascular effects

- After cranial RT , **36%** developed cerebrovascular complications as micro-bleeds and cavernomas MC
- Associated with RT dose to Circle of Willis, pre-pontine cistern and temporal lobes
- Rate of late occurring stroke was 267.5 /1 lakh persons, 29 fold ↑ than other cancer survivors

Moyamoya syndrome

- Non atherosclerotic stenosis of intracranial carotid a. in 3-4% pts
- Risk factors
- Age <10 years during RT
- RT volume involving the cranial base
- **RT to Circle of Willis, dose >50 Gy**
- Time interval after radiotherapy >5 years
- Neurofibromatosis-1
- Even 12 Gy can lead to risk of death

Protons reduce low & intermediate doses to vascular str. And also total RT dose to ant, middle , ant. communicating and carotid ↓by at least 25% and upto 100%



Denunzio 2020

Due to positioning of proton beams ant. To or in middle of spine in spinal CSI , exit dose to heart ↓by 4-8 folds

ENDOCRINE DYSFUNCTION

EPTN consensus

The EPTN consensus-based atlas for CT- and MR-based contouring in neuro-oncology 2018

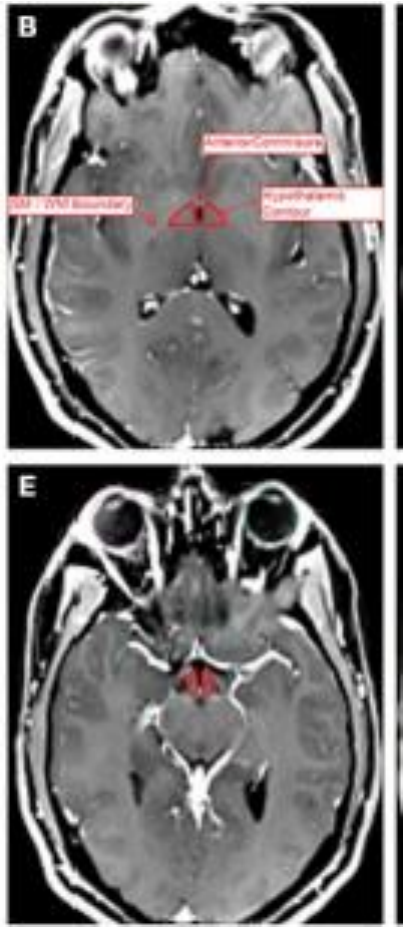
Eekers

Pituitary

Just inferior to the brain
Connected to the hypothalamus
by its pituitary stalk
Lat.- the inner part of the sella turcica
Use bone 1500/950 or soft tissue 350/50 WL/WW on CT.
Use sagittal view

Hypothalamus

2–4 cm_3,T1 weighted MR
Superior- ant.& post. commissure.
Inferior- base of 3rd ventricle or edge CSF within the suprasellar cistern
Post.- inter-peduncular fossa. Include the mammillary bodies
Medial – 3rdventricle or the visible CSF space.
Lateral- 3mm from the third ventricle.



Gonadal dysfunction

400 follicles released as oocyte during lifetime
<2 Gy- 50% immature oocytes destroyed
4-7 Gy- permanent ovarian failure
20 Gy- permanent ovarian failure
Early menopause at 31 yrs –CAD, bone loss
2-3 Gy- sperm production less
4-6 Gy- permanent azoospermia
12 Gy-increased LH
24 Gy to prepubertal testis- delayed puberty
33Gy- Leydig failure

Endocrine effects

< 1o Gy Total body RT - isolated GH deficiency
18–24 Gy cranial RT - Isolated GH deficiency
30 Gy -30-50% have the impairment of GH
>30 Gy -Gonadotrophin deficiency
>30 Gy-TSH and ACTH deficiency
>40 Gy-Precocious puberty
>40 Gy – Hyper-prolactemia
>45 Gy- Hypothyroidism, thyroid nodule, grave

Elson 2014 Front Oncol

Scoccianti,Radiotherapy and Oncology 128 (2018) 37–43

Money can't buy you everything but it can add to your comforts.

Endocrine effects less with protons

- Endocrine deficits in **43%** survivors
- Hypothalamus mean dose 16 Gy- 50% risk of GH deficiency
- Pituitary 30 Gy- 30% risk of GH deficiency

ACTH deficiency only 5% after >40 Gy RBE

Cranial RT

Protons ↓ mean doses than photons in Medulloblastoma pts
Hypothalamus- 27.6 Gy Vs 42.6 Gy
Pituitary- 24 vs 46.5 Gy
Thyroid- 0.10 vs 25.1 Gy

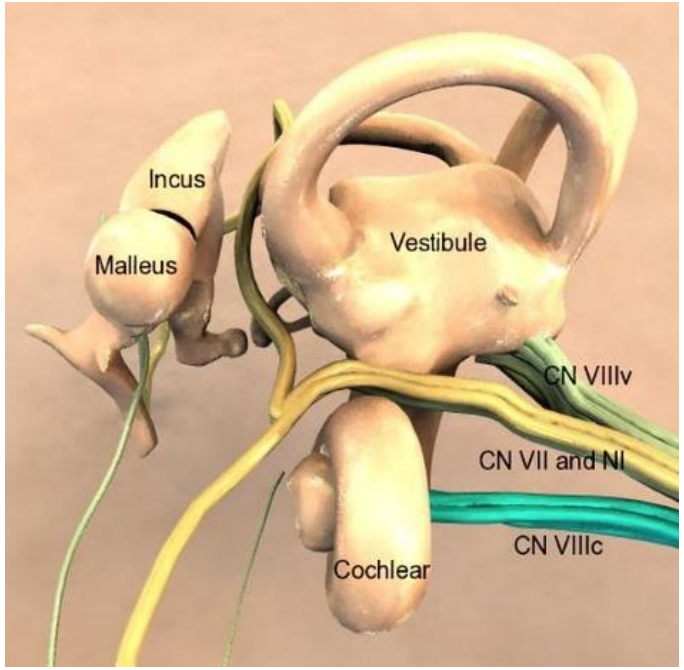
75 % reduction in GH deficiency and 85% ↓ in hypothyroidism

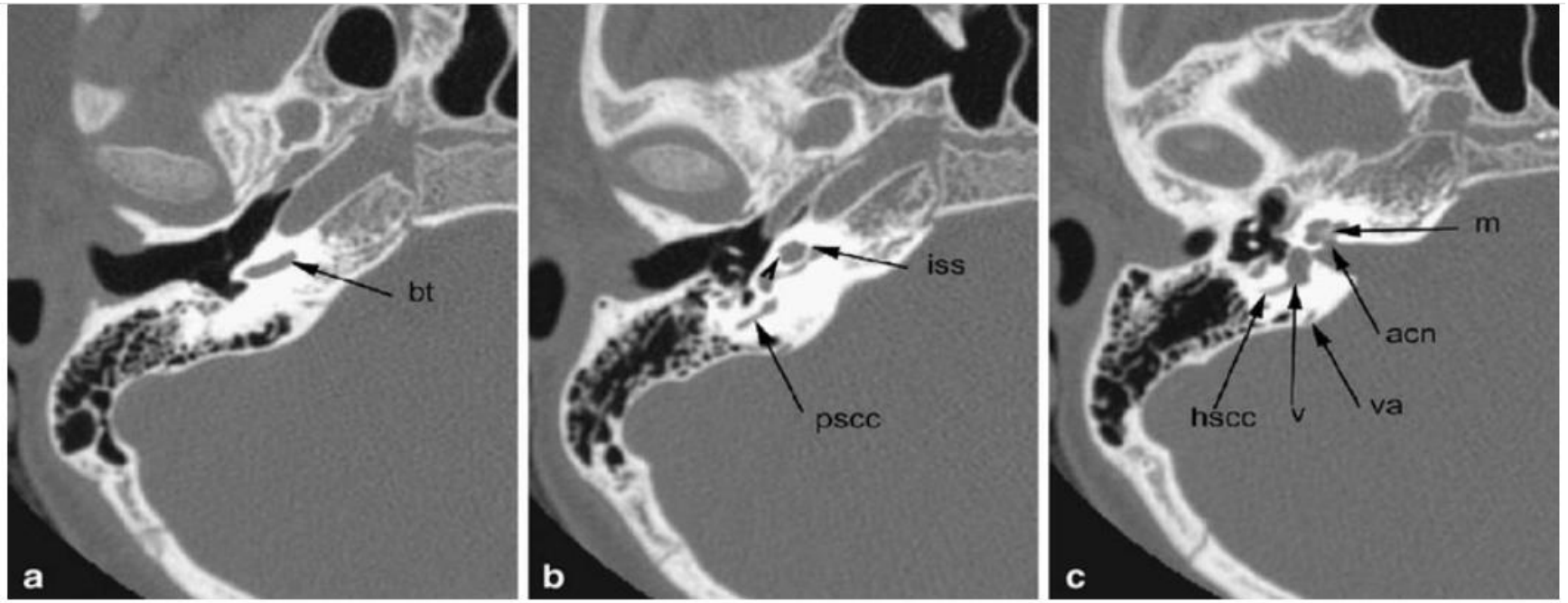
Partial volume effect for pituitary with endocrine dysfunction less if **dose < 50 CGE to ant part of gland.**
A post pituitary dysfunction with doses bw 50 CGE - 70 CGE not observed.

Gonadotrophin deficiency 5.1% after>40 Gy RBE

Baumert 2004, vatner 2018

How to identify auditory structures?





Use bone setting on CT, (WW/WL 20/1500). located lat and cranially of IAC, **T2 weighted image on MR**

Inner ear- Cochlea and IAC

Middle ear- Tympanic cavity and bony part of eustachian tube

Identify ear first. Identify Internal auditory canal

Cochlea ant and medial to it . Modiolus is the central part of cochlea.

Vestibule is medial to the tympanic cavity, post. to the cochlea and ant. to the semicircular canals.

Research | Open access | Published: 03 June 2023

The relevance of ototoxicity induced by radiotherapy

Yan Huang, Hong Zhou, Fenglan An, Aimei Zhao, Jian Wu, Meihua Wang & Judong Luo

Radiation Oncology **18**, Article number: 95 (2023) | Cite this article

Conductive hearing loss- due to damage to middle ear components, eustachian tubes or ossicles,
Sensorineural hearing loss (SNHL) –due to lesions in the cochlea or the auditory system's posterior section

Risk factors for ototoxicity

- Age- Children more
- Mean cochlear dose
- Technique of RT- IMRT less than 3DCRT
- Technology- less with protons
- Site of RT –Oropharynx < GBM< Vestibular schwannoma
- Time after RT
- Concurrent chemotherapy
- Cisplatin and carboplatin dose

Total hearing loss probability with mean cochlear dose
30-40 Gy -27%
40-50 Gy -28%
50-60 Gy- 35%
Children- mean cochlear dose < 30 Gy

High frequencies affected earlier

CTCAE

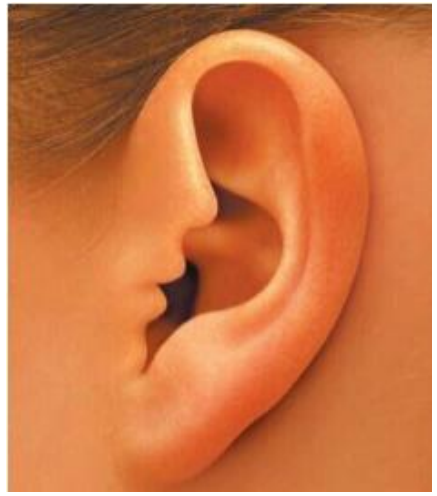
Grade 1: Threshold shift of 15–25 dB averaged at two contiguous frequencies
Grade 2: Threshold shift of > 25 dB averaged at two contiguous frequencies
Grade 3: Threshold shift of > 25 dB averaged at three contiguous frequencies
Grade 4: > 80 dB at 2 kHz and above

Brock criteria

Grade 0 to 1: < 40 dB on all frequencies or ≥ 40 dB at 8 kHz
Grade 2: ≥ 40 dB at 4 kHz
Grade 3 to 4: ≥ 40 dB at 2-1 kHz).

Arterial microvascular fibrosis and obliterative endarteritis in the blood vessels of the inner ear's ,degeneration and atrophy of the smooth muscle of the inner ear and the outer hair cells of the cochlea

Do protons help in decreasing cochlear dose as well?



- Sensori-neural hearing loss occurs over 3-5 yrs in pediatric pts. after Rx
- Factors associated are- cisplatin use, CSF shunting, cochlear dose >32-35Gy
- Vieira et al- no gr 3 toxicity
- if cisplatin dose <375 mg.ml
- median inner dose <42 Gy
- Huang et al- IMRT delivers mean auditory apparatus dose of 37 Gy while conventional RT gives 54 Gy with gr 3 hearing loss 13 vs 64% resp
- **Bass et al- hearing loss increased with cochlear dose from 2.7% for <40 Gy to 60% for >60-65 Gy**

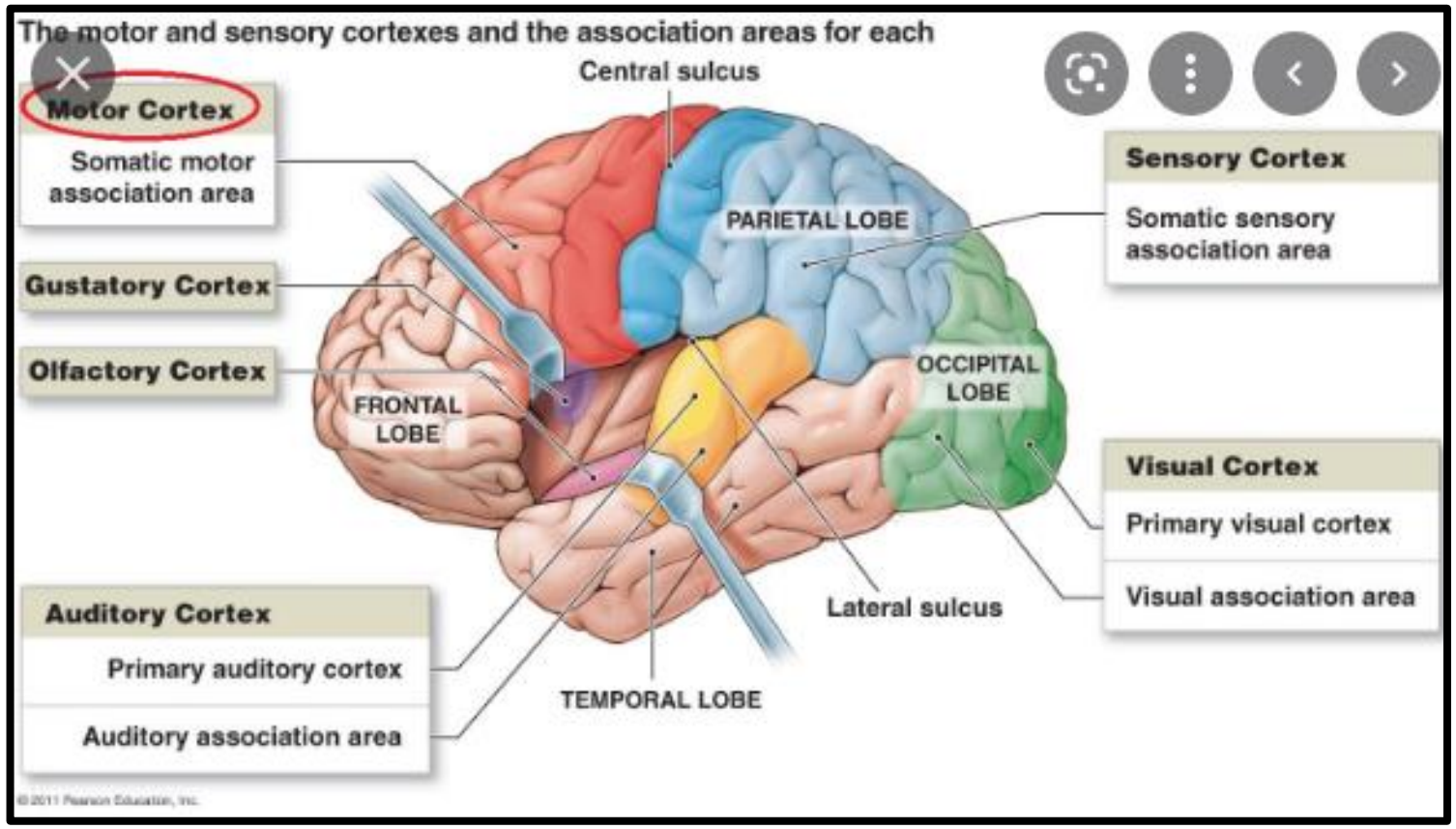
7% ↑ in sensorineural hearing loss with every 1 Gy ↑ in Mean cochlear dose.

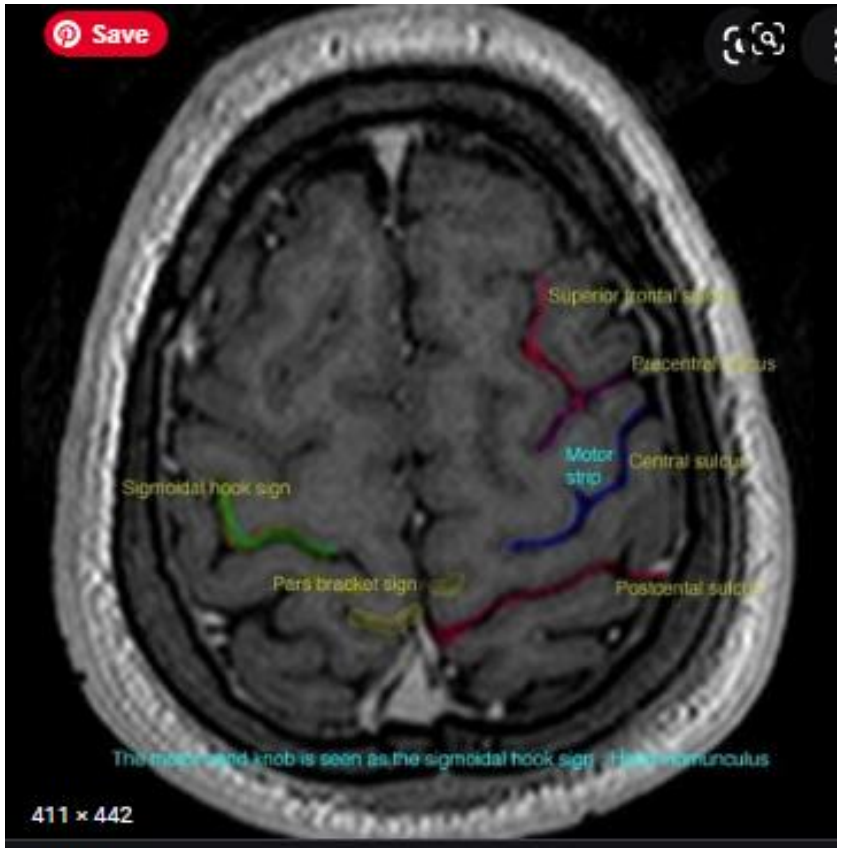
36% pts. have hearing loss after RT needing hearing aid

- ✓ **Rate of >20DB hearing loss ↓ by 50% with protons**
- ✓ **Cochlear dose↓ by 9 Gy with 54 Gy and 13 Gy with 59.4Gy with protons**
- ✓ >20 Gy DB hearing loss was 9±4% with protons vs17+-6% with 54 Gy with protons and 13±5 vs 23± 9% for 59.4 Gy
- ✓ In Cranio-pharyngioma pts. – mean cochlear dose with IMPT was 9.2 Gy with no cochlea receiving >40 Gy with 54 Gy, while with IMRT dose recd. was 18.8 Gy
- ✓ In HGG , IMPT cochlear dose 40.6 Gy and with IMRT it was 48.2 Gy

Fortin 2017J Neurooncol, Gondi 2016

MOTOR CORTEX





- Maruyama et al. -SRS of the corticospinal tract

  a **5% risk of complication V20Gy > 58mm3, V25 Gy >21 mm²**

- Pfeiffer et al- cognitive outcomes affected by the volume of the left hippocampus receiving 10 Gy and by the volume of the left precentral gyrus receiving 40 Gy

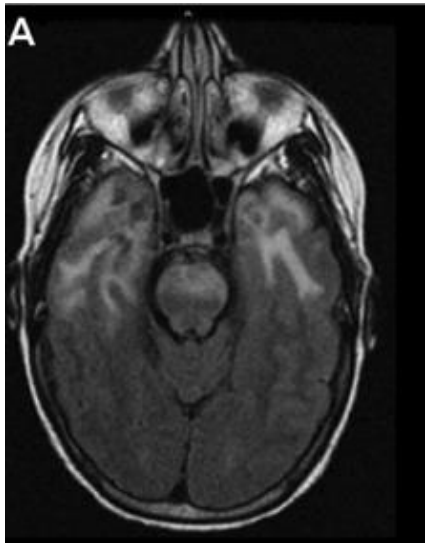
CEREBRAL RADIATION NECROSIS

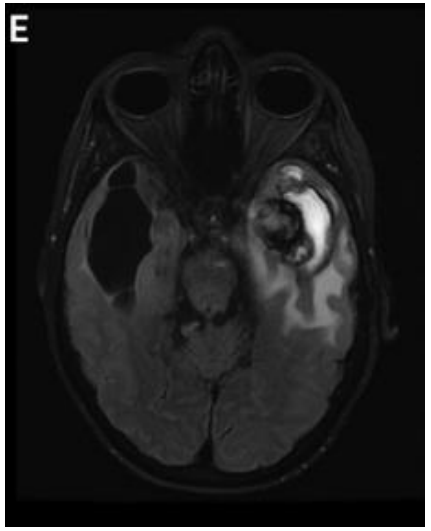
Incidence- Glioma-With CT/RT- 5% to 10% ,can be up to 50%
Nasopharyngeal ca.- 30-40 % of patients due to inclusion of temporal lobes
Onset- variable but may occur within the first year after RT

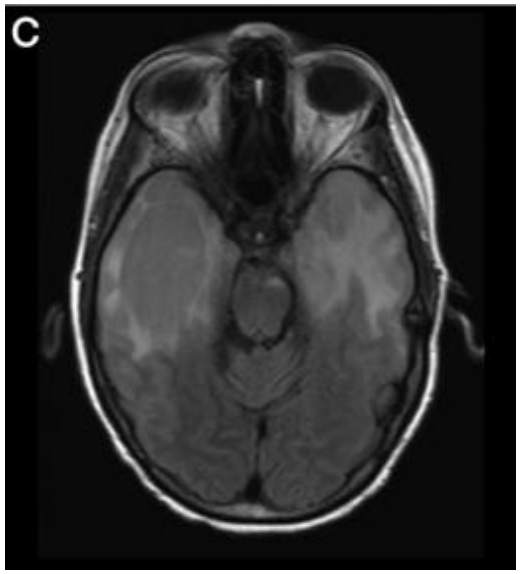
Risk factors –More with brachytherapy, SRS, CT/RT
Radiation dose
Radiation volume
Fraction size and schedule
Age
Presence of vascular comorbidities

MRI -focal areas of abnormal contrast enhancement on T1 ,T2 /FLAIR hyperintensities

Treatment- Biopsy/ resection







SECOND MALIGNANCIES

Def- histologically different from primary tumor and occurs 2 or more months after primary cancer within field of irradiated tissue

3% pts after 20 yrs FU and 8% after 30 yrs

Survivors 3-6 fold increased risk, 19 times increased risk of death due to 2nd malignancy

Depends on age at Rx, gender, family history of cancer, primary diagnosis

Protons- risk is 8 times less than IMRT and 17 times less than conventional RT

RT TECHNIQUE	% risk of 2nd Ca
IMRT	30
Electron Beam	21
Conventional RT	20
IM electron beam	15
PROTON (IMPT)	**4**

Predicted lifetime attributable risk with photons

2nd malignancy 4.6-10 fold ↑

Risk of mortality - 1.9 -5 fold ↑

Soft tissue 2nd cancer- 1.3-4.6 ↑

intracranial 2nd cancer -3.5- 9.5 ↑

MC- breast, bone, thyroid, brain

All pts.- meningiomas, high grade gliomas, astrocytomas

HL- breast cancer and thyroid

Abd. RT- colon polyps, colorectal cancer

Nonmelanoma skin cancer at entry and exit of RT beam

Indu Bansal, Paras Health, Gurugram

Acta Scientific Neurology 2019: 2(4), Arain 2015,Denunzio 2020

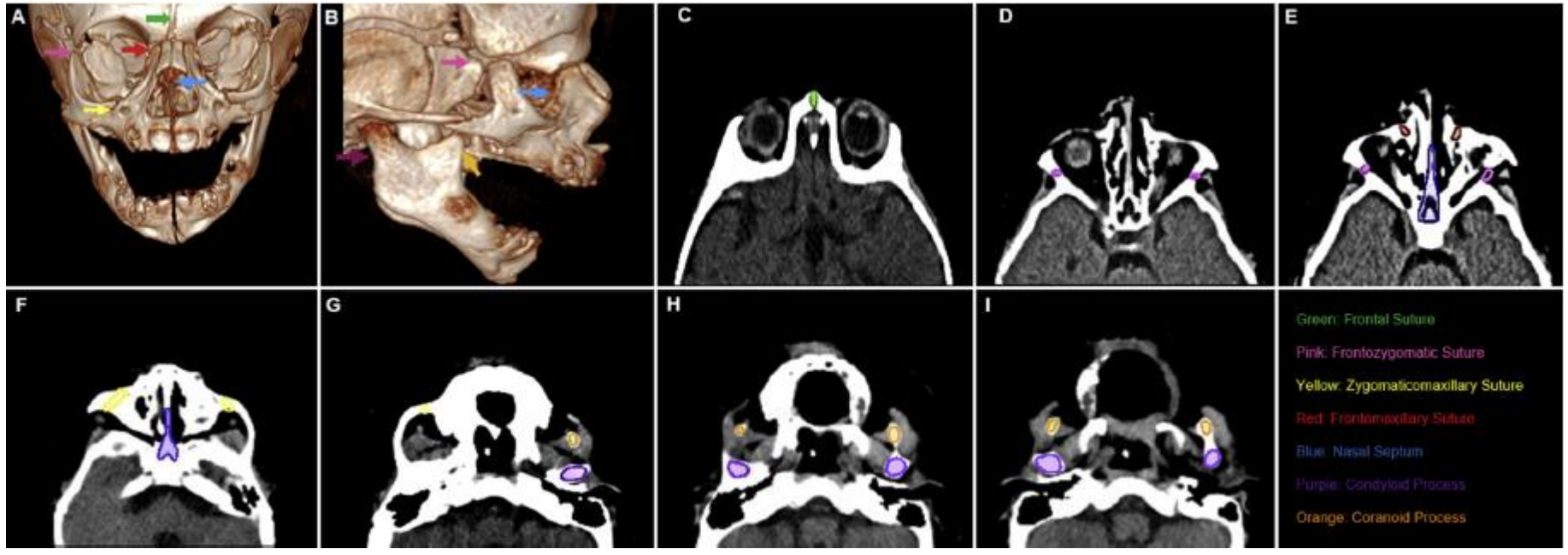
Cranial and craniofacial RT

Table 1 Percentage of craniofacial growth completion by age groups

Site	Patient age (y)		
	Birth-5 (%)	6-10 (%)	11-20 (%)
Cranium	85	11	4
Maxilla	45	20	35
Mandible	40	25	35

Adapted from Phulari.[28]

- Most of growth of calvarium within 1st yr and mostly completed by 5 yrs
- Cartilaginous nasal septum most imp driver of growth in maxilla and surrounding bones by 7 yrs of age. Hypoplasia may occur
- Nasopharynx- ⬇ interorbital distance



Indu Bansal, NH, Gurugram

Arain 2015

A Road Map for Important Centers of Growth in the Pediatric Skeleton to Consider During Radiation Therapy and Associated Clinical Correlates of Radiation-Induced Growth Toxicity

a-to-b ratio of growth plate- 4.5

Factors affecting growth

Age
Pubertal status
Nutritional status
Medical comorbidities
Systemic therapy
Surgical insults

RT factors

Total radiation dose
Fractionation
Dose homogeneity
Beam energy
Treatment volume
Symmetry of the treatment volume
Nature of the irradiated growth

Final height below 5th percentile in 10-15 % survivors >20 Gy cranial RT, early age, Females short stature
29-45 Gy GH deficiency

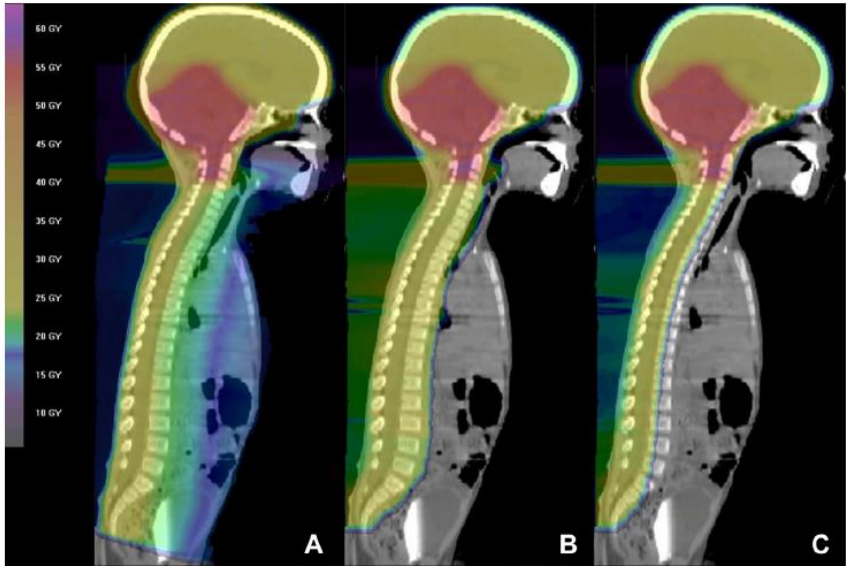
Axial skeleton matures a few years later than the remaining skeleton
Krasin et al- flat bones as facial and pelvis >35 Gy affects growth
Clavicle 15 Gy, Bone 25 Gy

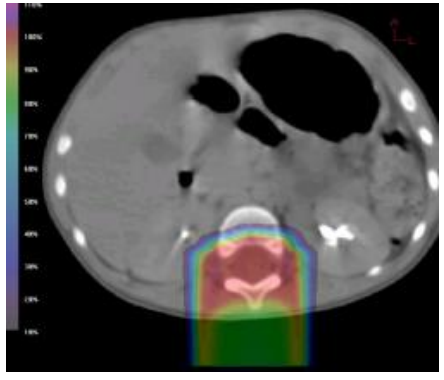
Restrict asymmetrical treatment to the **epiphyseal growth plates to <15 Gy.**

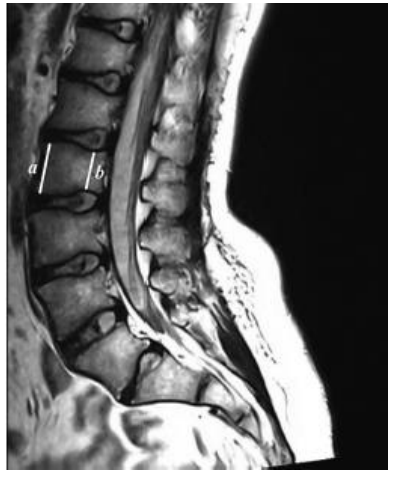
Indu Bansal, NH, Gurugram

Arain 2015

Effects of vertebral-body-sparing proton craniospinal irradiation on the spine of young pediatric patients with medulloblastoma







- Paulino in 2015 - Radiographic **scoliosis rate of 45% i**n medullo pts. treated with photon CSI despite inclusion of entire vertebral body.
- Vertebral body sparing CSI with protons did not increase severe spinal abnormalities
- Diminished growth of post. portion of vertebral body seen with an average posterior to ant. ratio of 0.88.
- Compensatory hypertrophy of post intervertebral discs
- Vertebral body sparing CSI spared around 46% active marrow
- Also esophagitis reduced from 35% with photons to 17% with protons
- VBS with IMPT decreases V10 and V20 of cervical & thoracic vertebrae

MacEwan 2017Adv in Radiat Oncol

Indu Bansal, Paras Health, Gurugram

Radiation necrosis

- After SRS range - 5% to 20%
- **Factors** -dose and tumor size.
- **Etiology**-CNS edema/inflammation leading to increased intracranial pressure, glial cell injury with neuronal demyelination, and vascular endothelial damage with resultant hypoxia leading to overexpression of vascular-endothelial growth factor (VEGF) and abnormal angiogenesis of small, leaky vessels

- Pts. may be asymptomatic, with mild radiographic edema, or they may have severe neurologic symptoms with enlarging, ring-like Contrast enhancement mimicking tumor progression.
- **Treatment**- Steroids, bevacizumab (a VEGF inhibitor) ,surgery, which may be preferred if underlying tumor progression is suspected. Immunotherapy may increase the risk of radiation necrosis

- **Pseudoprogression** - transient, weeks to < 6 months
- Occurs in ~21 - 31% of malignant gliomas treated with radiation and chemotherapy
- Significant mass effect & clinical neurologic deficits
- More in patient with MGMT methylation positivity
- More with protons
- Suggest a transient course with spontaneous recovery

- Progressive disease - recurrent / residual disease status post therapy
- **Pseudoresponse** - frequently observed in high grade glioma patients treated with angiogenesis inhibitors (e.g.. bevacizumab)

Brain health

Contribution of microbial immunity, stem cell biology,
Physical activity interventions
Development of novel strategies

Radiation Oncologists

Dosimetrists

Pharmacists

Neuro-psychologists

Improved caregiver and family support

Physical therapists

Nutritionists

Early and persistent intensive outpatient and inpatient rehabilitation

Exercise-induced stimulation of hippocampal neurogenesis, cognitive therapies and mesenchymal stem cell replacement

NEUROCOGNITIVE BATTERIES

Table 1 | Neurocognitive batteries used in modern prospective clinical trials.

Trial	Intelligence	Perception/psychomotor speed	Memory	Attention/executive function
EORTC	Dutch adult reading test	Line bisection test Facial recognition test Judgment of line orientation Letter-digit substitution	Working memory task Visual verbal learning test	Stroop color word test Categoric word fluency test Concept shifting test
RTOG 0614	COWA	Trail-making A	Hopkins verbal learning test	Trail-making B
RTOG 0933	N/A	N/A	Hopkins verbal learning test One card learning test International shopping list test	N/A
MDACC	N/A	N/A	Hopkins verbal learning test	N/A
CCOP 97100	COWA	Trail-making A	California verbal learning test Rey Osterrieth complex figure Digit span	Trail-making B

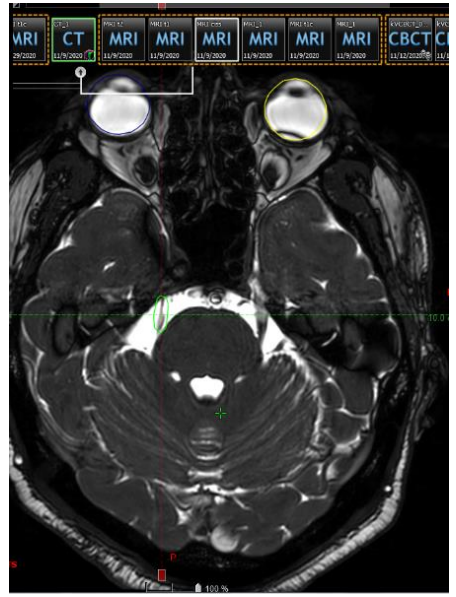
Frontiers 2012

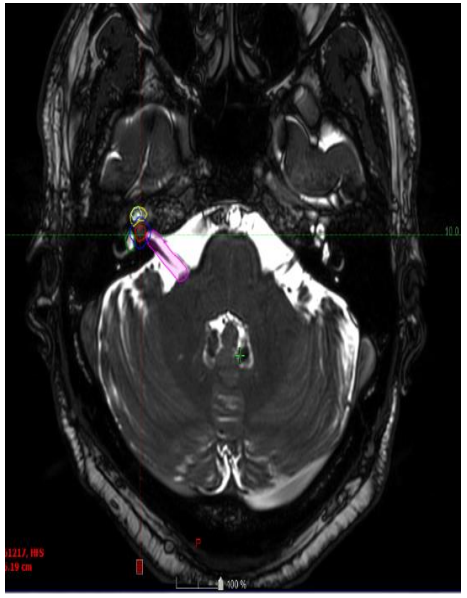
Organs at risk in the brain and their dose-constraints in adults and in children: A radiation oncologist's guide for delineation in everyday practice 2014

	Children	Adults	
Optic chiasm	Dmax < 54 Gy <60 Gy sec criterion	**D0.03 cc 55 Gy**	7% risk of optic neuropathy
Cochlea	Dmean < 35 Gy	Dmean < 45 Gy **Dmean 45 Gy** **Dmean 32 Gy**	
Hippocampus Hippocampal avoidance volume	D max < 6 Gy V3 Gy < 20% Dmax < 25.2 Gy and V20 Gy < 20% Dmax < 12 Gy V7.2 Gy < 40% Dmean < 30 Gy	**D40% 7.3 Gy** **Skin D0.03 cc 25 Gy**	In WBRT 100% of the hippocampus should not exceed 9 Gy, Dmax<16 Gy in 10 Fractions.
Brainstem	Dmax < 54 Gy Dmax < 60 Gy D59 Gy < 10 cc	Surface D0.03 cc 60 Gy Interior D0.03 cc 54 Gy **Brain V60 Gy 3 cc**	
Pituitary gland	Dmax < 50 Gy Dmean < 25 or 30 Gy	Dmax < 60 Gy Dmax < 42 Gy **Dmean 45 Gy, Dmean 20 Gy**	
Retina		Dmax < 45 Gy Dmax < 50 Gy **D0.03 cc 45 Gy**	
Lacrimal gland		V30 Gy < 50% Dmax < 40 Gy, **Dmean 25 Gy**	
Lens		Dmax < 6 Gy Dmax < 10 Gy D0.03 cc 10 Gy	

Radiation dose constraints for organs at risk in neuro-oncology; the European Particle Therapy Network consensus 2018

Trigeminal nerve





Facial nerve

Indu Bansal, Paras Health, Gurugram

Constraints for normal organs

	Kandula 2014	COG
I/L kidney	100% vol- <14.4 Gy 50% Vol- <19.8 Gy	100% < 18 Gy, 14.4 75% <18 Gy Mean dose < 18Gy
C/L kidney	100% vol- <14.4 Gy 80% vol- <12 Gy 50% vol- < 8 Gy	<25 % >18Gy
Liver	100% vol- < 18 Gy 75% vol- <18 Gy 50% vol- < 9 Gy	<15% > 30 Gy Mean dose < 15 Gy
Spleen	30 Gy- asplenia	
Vertebral bodies (if included in PTv)		Minimum dose 18 Gy to entire corpus and pedicles
B/L lungs		< 30% > 20 Gy
i/L lung		<30% > 20 Gy
C/L lung		<10% > 20 Gy
Lens	**GOG ARST1431**	100% 14.4 Gy
Spinal cord		Any volume <45 Gy
Optic n, chiasm		100% <54Gy
Eye		100% < 45

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OAR constraints for vestibular schwannoma

Brainstem- QUANTEC 12.5 Gy (< 5 % neuropathy or necrosis)
TG101 1F- < 15 Gy, 3 F- < 23.1 Gy, 5 F < 31 Gy
1F- < 12 Gy, 3 F- < 21 Gy, 5 F < 30 Gy

Chiasm- 8 Gy (< 10% optic neuropathy)
Spinal cord – 13 Gy (< 1 % myelopathy)
Brain V12 < 5-10cc (< 20 % sympatomatic necrosis)

Cochlea/Modiolus – QUANTEC 14 Gy (< 25 % sensory- neural hearing loss)
TG 101- 1F- 9 Gy, 3 F- 17.1 Gy, 5 F- 25 Gy
Linskey 2013, ventral cochlear nucleus of brainstem- < 9 Gy
Modiolus and basal turn of cochlea- < 5.3 Gy, possibly < 4.2 Gy
Vestibule- < 5 Gy
Labyrinth – 10 Gy
Trigeminal nerve – 18 Gy

Facial n preservation after GK- 96.2 %
Dose- <13 Gy- 98.5 %
>13 Gy- 94.7%
Tu volume < 1.5 cm3- 99.5%
> 1.5 cm3- 95.5%
Age
< 60 yrs- 96.8%
> 60 Yrs- 89.4%
Friedman- **1cc increase in tumor- 17% increase in toxicity**
2.5 Gy increase in dose- 8 x toxicity

Don’t undertreat tumor in distal fundus
Don’t reduce margin prescription dose to achieve lower cochlear dose
Pre-treatment hearing and marginal dose , mean dose to cochlear vol imp

National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury

Proposed constraints

Photons	Protons
• D50<61Gy max <62Gy	<52.4 max <54
• D10-<63Gy max-<64Gy	<58 Gy
• D0.1cc-	<56.6

University of Florida
New constraints

- **D max 0.1cc<56.6GyRBE**
- **D50% <51.4 Gy RBE**
- **D10% <55.4Gy RBE**
- **No plan should exceed Dmax**
- **2 of 3 dose matrix to be met in all**

- ✓ Limit initial CTV expansion to 3mm in depth within brainstem
- ✓ Obligatory reduce CTV after 54GY, then 5.4 Gy with brainstem sparing
- ✓ MDACC- Avoid distal dose fall off and overlap of > 1 beam in spinal cord or brainstem
  Avoid >1/3 of beams ending in common brainstem tissue outside PTV (Florida)
- ✓ MGH- Prescription doe 54Gy RBE(max 55.5Gy)
  Spinal cord dose-<50.4Gy, %2 Gy at SC- brainstem junction
  No hotspots - 55.5 Gy (RBE) in brainstem
- ✓ PA and rt oblique fields at25 degrees to normal
- ✓ Smear distal beam edge to avoid high dose areas caused by Braggs peak higher biological dose

Indu Bansal, NH, Gurugram

Haagan 2018

TOXICITY SCORING CRITERION

Table 5. RTOG and EORTC central nervous system toxicity tables

1	2	3	4
Acute toxicity grade: brain			
Fully functional status (i.e., able to work) with minor neurological findings; no medication needed	Neurological findings sufficient to require home care; nursing assistance may be required; medications including steroids and anti-	Neurological findings requiring hospitalization for initial management	Serious neurological impairment that includes paralysis, coma, or seizures > 3 per week despite medication and/or hospitalization required
Chronic toxicity grade: brain			
Mild headache; slight lethargy	Moderate headache; great Lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizure or paralysis; coma
Chronic toxicity grade: spinal cord			
Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treated	Monoplegia, paraplegia, or quadriplegia

Grade 0 toxicity, none; grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life threatening; grade 5, fatal.
Data from Cox et al.[68]

TREATMENT FOR RT INDUCED BRAIN INJURIES

- Symptomatic treatment
- Oral corticosteroids for symptomatic cases
- Resection with frozen section diagnosis
- No known medical therapy for cognitive impairment
- Hippocampal avoidance strategies
  - Stereotactic conformal radiotherapy
  - Intensity modulated radiotherapy
  - Proton beam therapy

Prevention is the key

Potential therapies under investigation

- Antiplatelet and anticoagulation
- Reactive oxygen species (ROS) scavengers
- Improving microcirculation: butylphthalide
- Neurogenesis: neural stem cell therapy
- Renin angiotensin system inhibitors
- Anti-VEGF antibody
- Hyperbaric oxygen treatment
- Exercise
- Small molecule compounds targeting p53 isoform Δ133p53α
- Peroxisomal proliferator activated receptor agonists
- Memantine
- Lithium

IntechOpen: 2023, Neurooncol Adv 2020,Front Oncol 2012;2:73

Monitoring of childhood survivors

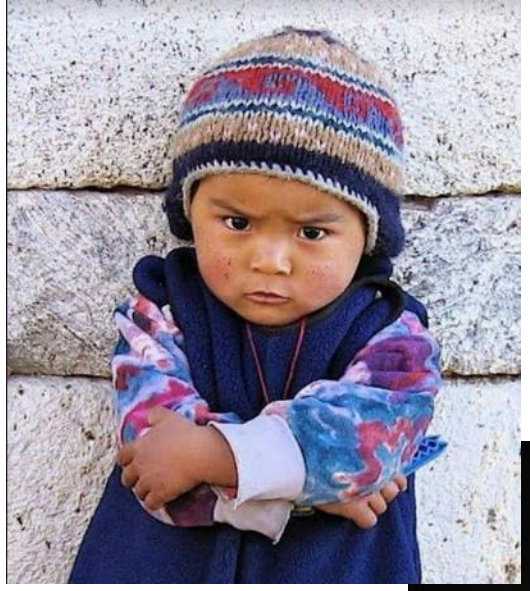
- CBC annually x 10 yrs because of increased risk of leukemias
- TSH and T4 screening yearly if RT to head and neck and mediastinum
- Semen analysis with LH, FSH, testosterone for males, pubertal status
- LH, FSH for females
- Lipid profile annually if TBI or cranial radiation
- Cardiac monitoring ECG, ECHO frequently, monitor females for cardiac complications during pregnancy
- MR angiogram annually if >50 Gy to prepontine cistern
- Discuss sexual dysfunction and other psychological issues and provide job opportunities, encourage social interactions
- Begin growth hormone therapy 2 years after diagnosis in whom have a decline

COG guidelines, Duffner 2004

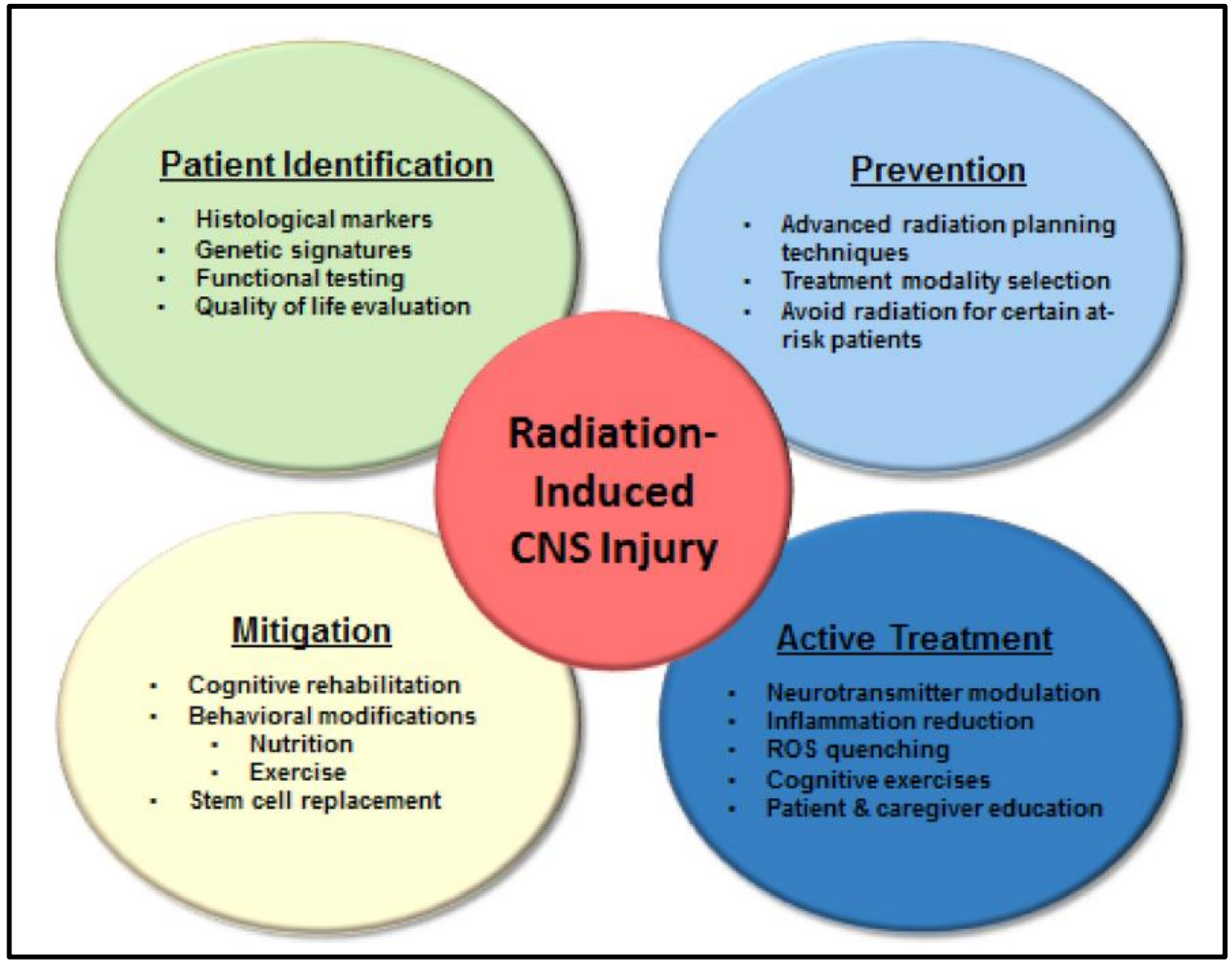
MY TAKE HOMES ….

Pressing need for improved understanding of the biology related to the combined effects of tumor, pharmacological therapies, and radiotherapy on short term and late changes in brain microenvironment, neuro-immunity, neural circuitry and pathways, blood-brain barrier permeability, as well as subcellular mechanisms of neurological dysfunction and neurodegeneration.

- Protecting subcompartments of brain responsible for neuro-toxicity is the key as hippocampus
- Effective radioprotectors, compounds which act as radiation modifiers to reduce the damage of ionizing radiation on normal tissue, have not yet been identified.
- Memantine and Donezepil have demonstrated some efficacy.
- Protons, have theoretical advantages in limiting the amount of normal tissue exposed to ionizing radiation
- Imaging-related biomarker identification for normal tissue injury and response in patients receiving radiation is one area of investigation that may show potential promise.



Take gentle care of your little friends



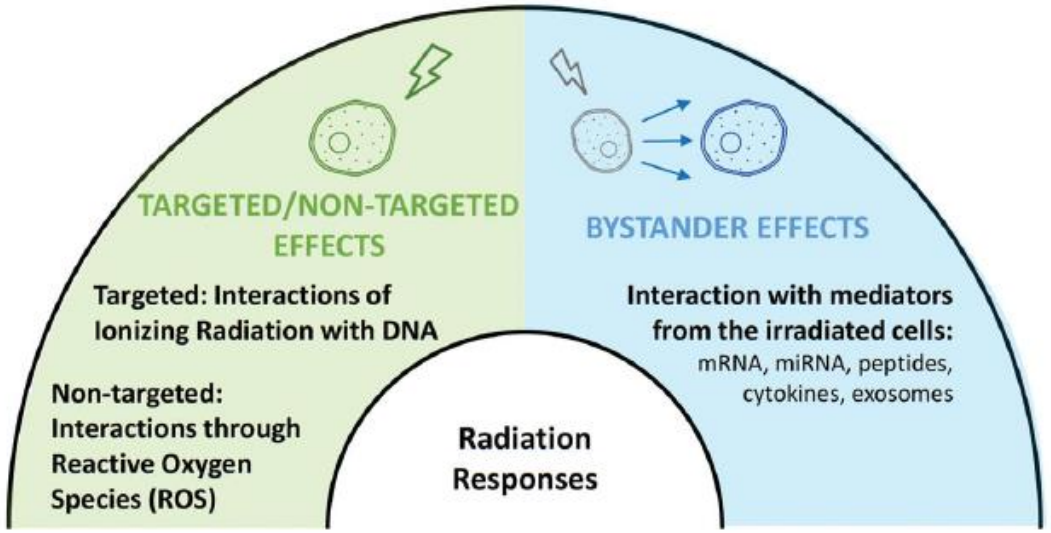
The acute CNS syndrome occurs after single doses >30Gy; white matter necrosis occurs at fractionated doses >60Gy

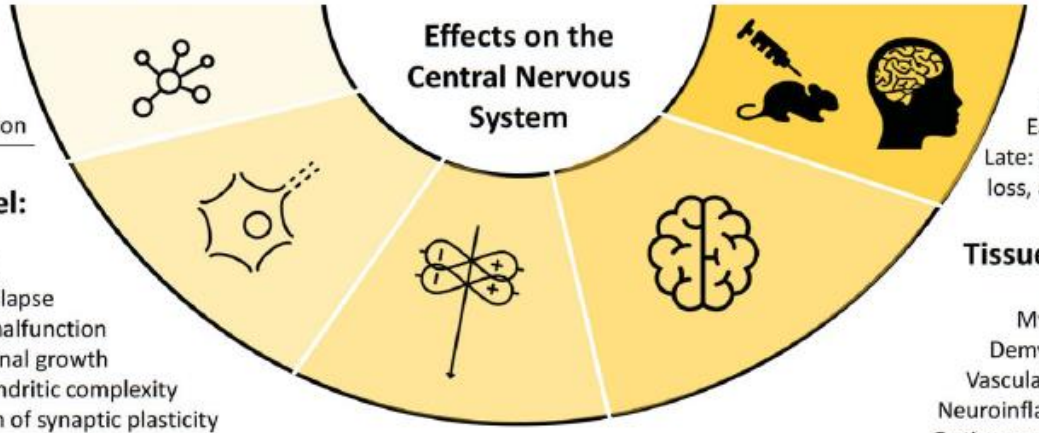
RANDOMISED TRIALS TO PREVENT CNS TOXICITY

Trial	Intervention	Mechanism	Administration	Result
RTOG 9104[21]	Hyperfractionation	Altered fractionation	54.4 Gy/1.6 Gy BID vs. 30 Gy/3 Gy	- No significant difference on MMSE at 3 months - Tumor control correlated to better MMSE scores
RTOG 0933[42]	Hippocampal sparing	Preservation of hippocampal neurogenesis	Intensity modulated radiation therapy (IMRT) delivered as 30 Gy in 10 fractions	- Reduced mean relative decline in the HVLT-R DR (7% vs. 30%, $p<0.001$)
N0574[43]	SRS vs. WBRT	Reduction of treatment volume	SRS (18–24 Gy) +/− Whole brain irradiation (30 Gy/12 fractions)	- SRS alone associated with less cognitive decline at 3 months (63.5% vs. 91.3%, $p<0.001$) - For long-term survivors, SRS alone benefitted cognitive function both 3 months (45.5% vs. 94.1%, $p=0.007$) and at 12 months (60% vs. 94.4%, $p=0.04$)
RTOG 0614[46]	Memantine	NMDA receptor antagonist	20 mg/day given during radiation and for 24 weeks post-radiation	- Increased time to cognitive decline (HR 0.78, $p=0.01$) - Reduced probability of cognitive function failure at 24 weeks (53.8% vs. 64.9%)
Wake Forest[47]	Donepezil	Acetylcholine esterase inhibitor	5–10 mg/day for 24 weeks beginning at least 6 months after partial or whole brain irradiation	- No difference in composite score - Improved memory ($p<0.05$) - Improved motor speed and dexterity ($p=0.016$) - Greater benefit with baseline neurologic impairments

Semin Radiat Oncol. Author manuscript; available in PMC 2018 October 01.

RT INDUCED RESPONSES OF CNS





Molecular Level:
DNA damage
Reactive Oxygen Species generation
1-4

Cellular Level:
Cell death
Cell cycle arrest
Growth cone collapse
Mitochondrial malfunction
Inhibition of axonal growth
Reduction of dendritic complexity
Down-regulation of synaptic plasticity
5-16

Electrophysiological Level:
Alteration of dendritic excitability
Neuron depolarization
Loss of dendritic spines
17-24

Tissue Level:
Gliosis
Myelopathy
Demyelination
Vascular damage
Neuroinflammation
Optic nerve damage
Inhibition of neurogenesis
Increased blood-brain barrier permeability
Inhibition of cell proliferation and differentiation
25-46

Behavioral Level:
Acute: anorexia, nausea, edema, headache
Early delayed: somnolence, attention deficit,
Late: gait disturbance, hypolocomotion, memory loss, anxiety, paralysis, dementia, death, distress
47-60

Pariset 2020

RECOMMENDATIONS FOR RT DOSE

Table 3. Tolerance doses for normal central nervous system tissues*

CNS tissue	TD 5/5 (Gy)	TD 50/5 (Gy)	End point
Rubin, et al.			
Brain			Infarction, necrosis
Whole	60	70	
Partial (25%)	70	80	
Spinal cord			Infarction, necrosis
Partial (10 cm length)	45	55	
Emami, et al.			
Brain			Infarction, necrosis
One-third	60	75	
Two-thirds	50	65	
Whole	40	60	
Brainstem			Infarction, necrosis
One-third	60	–	
Two-thirds	53	–	
Whole	50	65	
Spinal cord			Myelitis, necrosis
5 cm	50	70	
10 cm	50	70	
20 cm	47	–	
Cauda equine	60	75	Clinically apparent nerve damage
Brachial plexus			Clinically apparent nerve damage
One-third	62	77	
Two-thirds	61	76	
Whole	60	75	

Normal tissue	TD 5/5 (Gy)	TD 50/5 (Gy)	Manifestations of severe injury
Ear (middle/external)	30–55	40–65	Acute or chronic serous otitis
Eye			
Retina	45	65	Blindness
Lens	10	18	Cataract formation
Optic nerve or chiasm	50	65	Blindness

Data from Emami et al.,[57] Sklar and Constine,[65] Gordon et al.,[66] and Cooper et al.[67]

Table

Medications for neurocognitive disorders

Medication	Class	FDA indication	Dosing
Donepezil	Cholinesterase inhibitor	Mild to severe cognitive impairment	5 mg/d for 4 to 6 weeks, titrate to 10 mg/d. Limited evidence supports 23 mg/d for patients who have been taking 10 mg/d for 3 months
Galantamine	Cholinesterase inhibitor	Mild to moderate memory impairment	IR: 4 mg twice a day with meals, titrate to 8 to 12 mg twice a day as tolerated ER: 8 mg/d with meal for 4 weeks, then titrate to 16 mg/d for 4 weeks, then titrate to 24 mg/d
Rivastigmine	Cholinesterase inhibitor	Mild to moderate memory impairment	1.5 mg twice a day for 2 to 4 weeks. Titrate by 1.5 mg twice a day every 2 to 4 weeks to 3 to 6 mg twice a day
Memantine	NMDA receptor agonist	Moderate to severe memory impairment	5 mg at bed, titrate by 5 mg at weekly intervals until reaching 10 mg twice daily XR: 7 mg/d, titrate by 7 mg at weekly intervals to 28 mg/d

Source: References 6-10

ER: extended release; FDA: Food and Drug Administration; IR: immediate release; NMDA: *N*-methyl-D-aspartate; XR: extended release

Simultaneous integrated protection

A new concept for high-precision radiation therapy

Thomas B. Brunner[1,2] · Ursula Nestle[1,2] · Sonja Adebahr[1,2] · Eleni Gkika[1,2] · Rolf Wiehle[1,2] · Dimos Baltas[1,2] · Anca-Ligia Grosu[1,2]

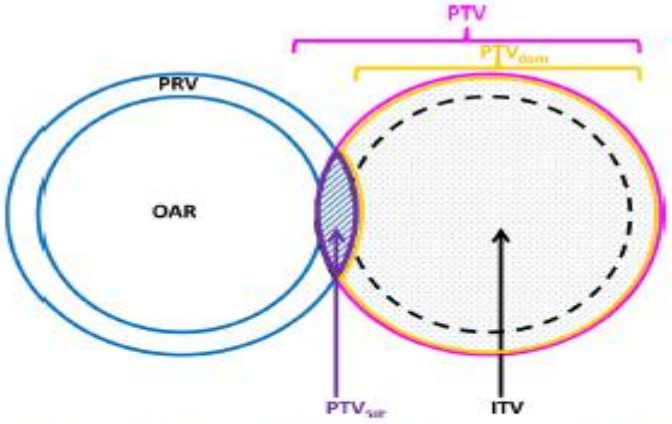
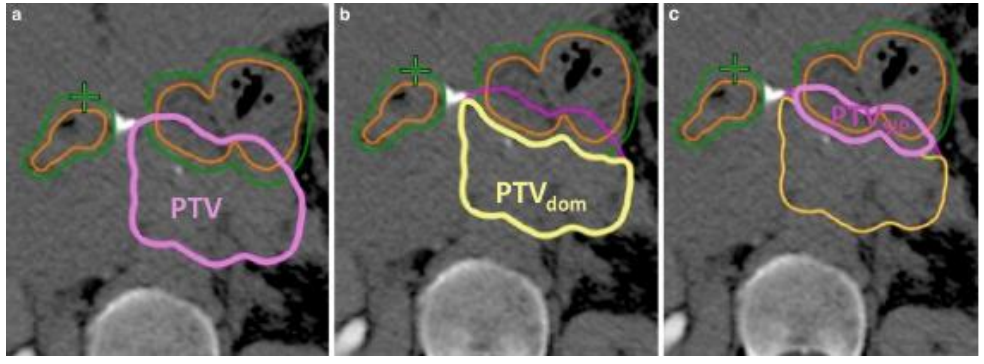


Fig. 1 Contouring and planning using the simultaneous integrated protection (*SIP*) concept. Scheme of a critical organ at risk (*OAR*; *blue, left side*) with its planning risk volume (*PRV*) overlapping with the planning target volume (*PTV*, *pink*). The dominant PTV (PTV_{dom} = PTV\PRV; *orange*) is the prescribed dose in the conventional way, whereas the PTV_{SIP} (=PTV ∩ PRV; *purple*) is prescribed a lower dose to stay within the dose constraints for the OAR



The SIP concept combined with a simultaneous integrated boost (SIB)
For PTV SIP, i. e., the volume that contains the dose gradient from PTVdom to the OAR(s), the planning instructions were twofold:
1) to stay within the boundaries of the given dose constraints for the OAR itself
2)to make use of the maximum possible dose to PTVSIP to minimize dose inhomogeneity for PTV. SIP concept is proposed for serial OARs according to the model of functional subunits for serial organs, e. g., spinal cord, esophagus, and bowel

Strahlenther Onkol (2016) 192:886–894