

# Long Term Effects of Cranial Radiotherapy

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# Definition

- acute effects: during radiation and/or up to six weeks afterwards
- early-delayed effects: six weeks to six months after radiation, and
- late effects: six months or more after the completion of radiation

# Pathophysiology

- vasculature of the brain as well as the direct effects on neuroglial cells and their precursors, including stem cells [[1](#)]. In addition, inflammation and blood-brain barrier disruption, induced by radiation, may also cause direct or indirect cellular damage

# Pathophysiology

- Vascular endothelial cell damage  
Fibrinoid necrosis of small vessels

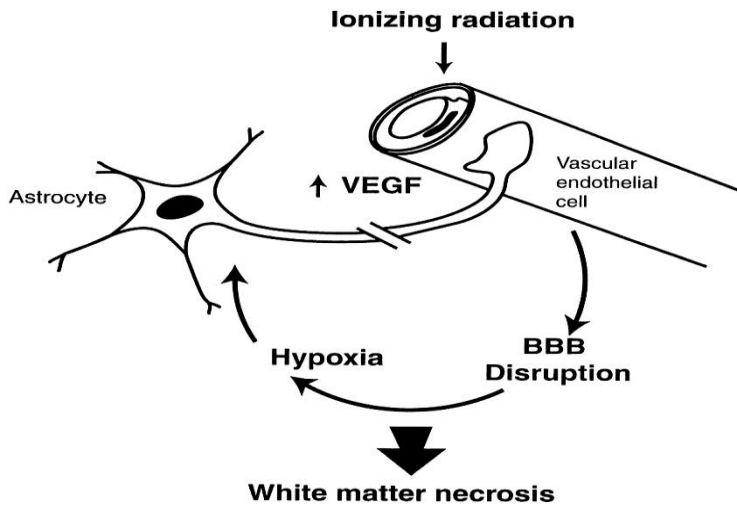
Capillary Leakage

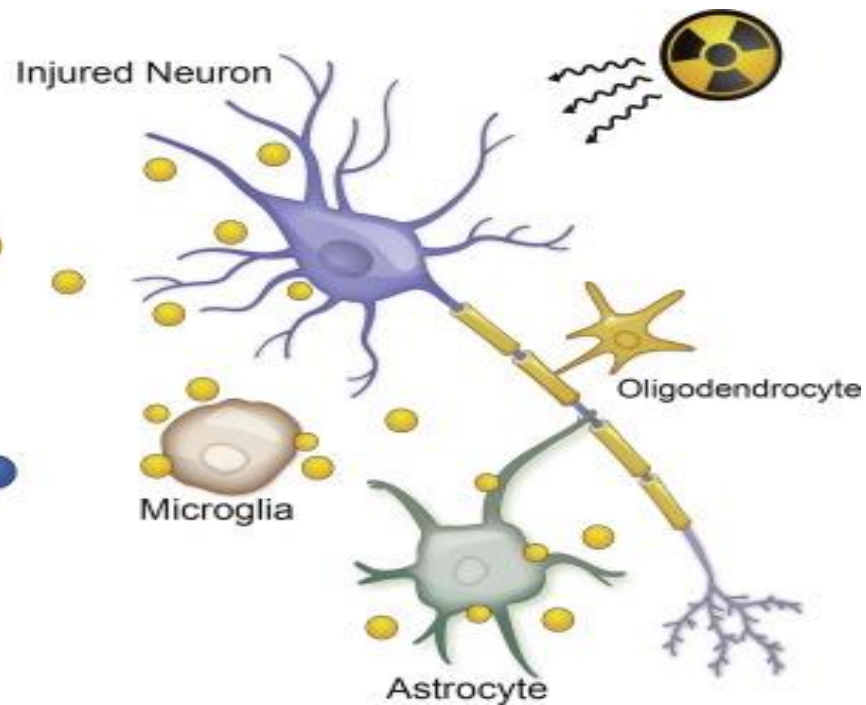
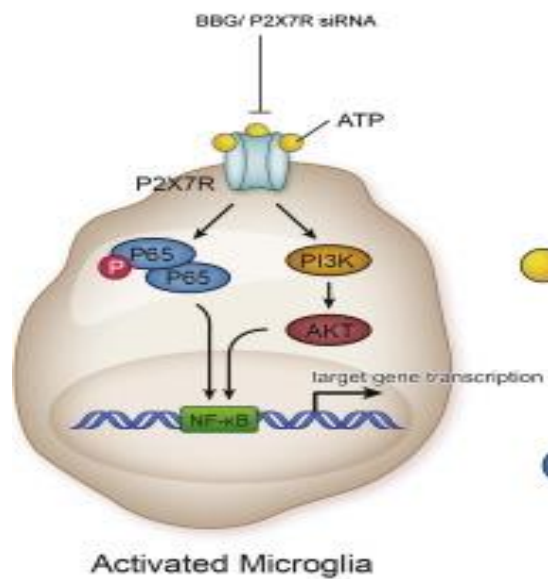
Demyelination of brain

VEGF released in

to hypoxia further

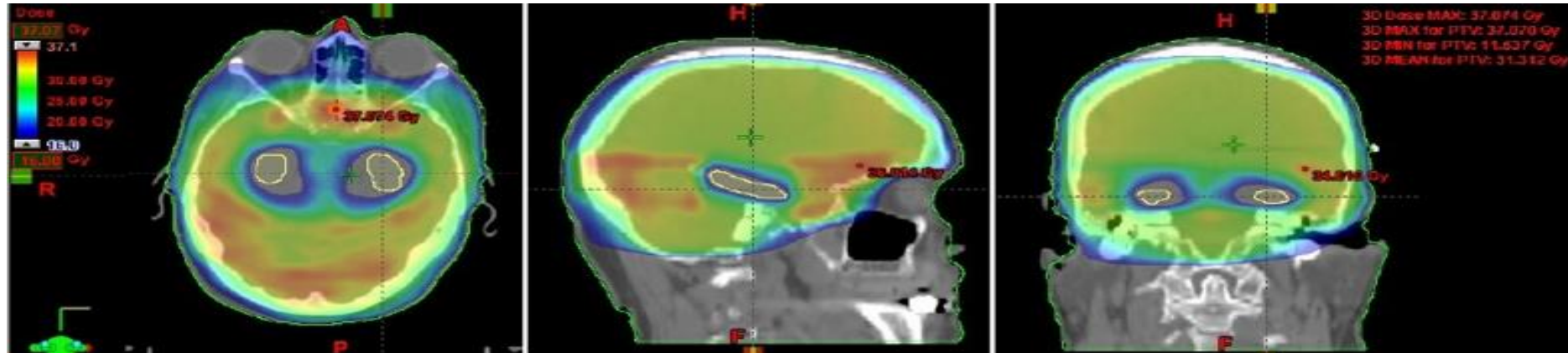
disrupts BBB





# Proliferating Neuroglial Progenitor Cells

- Evidence suggests that radiation is cytotoxic to proliferating neuroglial progenitor cells
- Loss of neurogenesis could lead to delayed cognitive deficits... rationale for hippocampal avoidance



# Risk Factors

Volume of Brain Treated

Total Radiation Dose

Dose Per Fraction

Concurrent Medications

Underlying Host Variables (e.g. age, genetics, comorbidities)

# Radiation Necrosis

- Onset: Typically 1-3 years after radiation
- Dose Threshold: 5% risk at about 72 Gy (@ 2 Gy/fraction)
- Higher incidence after SRS or when systemic therapy is used concurrently
- Symptoms range from focal to generalized deficits, mild to severe



# Radiation Necrosis: Diagnosis

- Diagnosis difficult by imaging, hard to differentiate necrosis from recurrent tumor
  - Typical MRI appearance = enhancing lesion with central necrosis and reactive edema
  - Lack of mass lesion and/or high proportion of edema suggestive
  - Test of time may help
  - Advanced technology may help
    - Perfusion-weighted MRI
    - Diffusion-weighted MRI
    - Magnetic Resonance Spectroscopy
    - PET
- Biopsy may be needed for definitive diagnosis

# Radiation Necrosis: Treatment

- Self-limited and low grade in many cases
- Initial treatment: Steroids (4-8 mg PO Decadron daily)
- Steroid refractory patients may be treated with Bevacizumab or interstitial laser thermal therapy
- Surgical resection reserved for diagnosis or medically refractory patients

# Neurocognitive Effects

- Early-delayed: 3 months – 1 year
  - Numerous studies on whole brain radiotherapy show >5 point drop in Hopkins Verbal Learning test scores (Short term recall and verbal fluency) and worsened QoL outcomes at 4 month time points, which persist up to 1 year
- Long term effects: 1 year or longer
  - Difficult to study because population has poor prognosis and there are multiple potentially confounding variables (chemo, surgery, baseline function, comorbidities, etc.)
  - Diffuse white matter changes seen for nearly all patients receiving whole brain RT doses of > 20 Gy ; severity of symptoms correlate with degree of radiographic changes
  - When severe, could lead to ataxia, confusion, memory loss, dementia, and rarely death

# Neurocognitive Effects: Evaluation

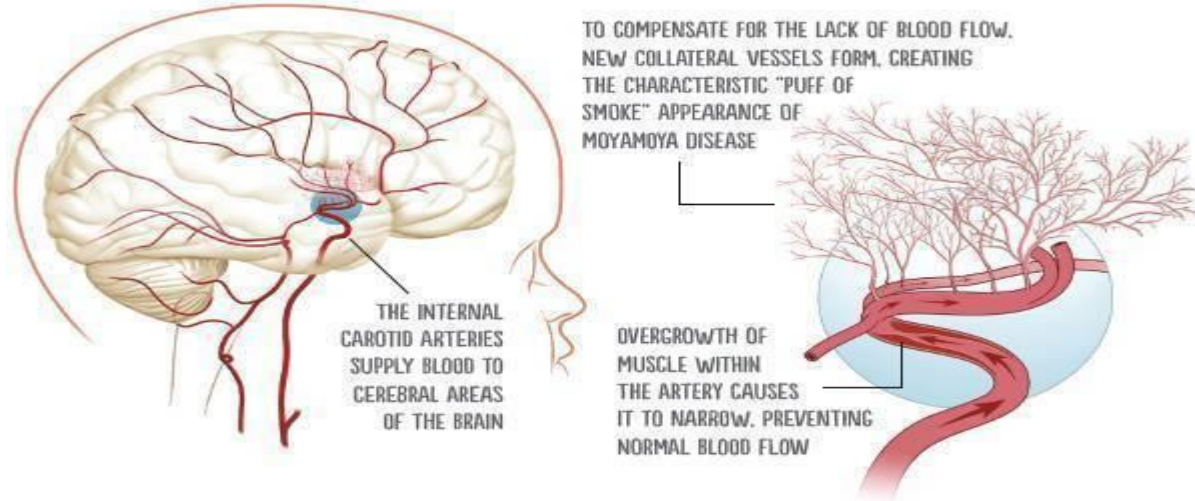
- Thorough history and physical to identify and treat contributing factors
- Formal neurocognitive and neuropsych testing usually not necessary unless it is needed to establish a baseline (e.g. neurocognitive rehab is planned)
- Important to review imaging as potentially reversible causes of cognitive decline include brain tumors and hydrocephalus
- Rarely vitamin deficiencies, metabolic abnormalities, or thyroid dysfunction may be the culprit

# Neurocognitive Effects: Treatment

- Pharmacologic interventions have been tested in randomized trials with mixed results
- Individualize treatment decisions:
  - Methylphenidate and Modafinil may be preferential for patients with profound fatigue or poor motivation
  - Donepezil or Memantine for patients with prominent memory impairment

# Cerebrovascular Effects

- Occlusive or hemorrhagic stroke, cavernous malformations
- Children more susceptible, supraclinoid region of the internal carotid artery and the circle of Willis are especially vulnerable



# Radiation Induced Visual Disturbance

- **Cataracts** – low doses to the lens (50% develop after 10 Gy), 2-8 years after treatment, correlated with steroid use
- **Optic Neuropathy** – painless monocular or bilateral impairment, 6-24 months after treatment. Dependent on dose and fractionation
  - <55 Gy: incidence unusual
  - 55-60 Gy: 3-7% incidence
  - >60 Gy: 7-20%
- **Xerophthalmia** – correlated w/ dose to lacrimal gland, increases w/ doses > 30 Gy
- **Retinopathy** – correlated w/ dose to retina, use of chemo, and presence of diabetes. Dose threshold around 45 Gy

# Ototoxicity

- **Acute:** Tinnitus and High Frequency Hearing Loss occasional occur. Related to otitis media and Eustachian tube edema. Symptoms resolve spontaneously but myringotomy may be needed for symptom relief
- **Late:** Sensorineural damage correlated with age, use of cisplatin, and dose to cochlea (~35 Gy dose threshold)
  - Cochlear implant can be considered



# Endocrinopathies

- Hypothalamus and pituitary dysfunction:
  - Dose threshold about 20 Gy
  - Variable time course, abnormal serum hormone levels typically long precede clinical symptoms
  - Baseline post-treatment and annual bloodwork to screen for dysfunction
  - Most common abnormalities (in decreasing order): GH, GnRH, Prolactin, ACTH, TSH

# Radiation Induced Malignancy

- Meningiomas, gliomas, nerve sheath tumors, sarcomas
- Risk proportional to radiation dose
- Very rare, but Likely that number of cases will increase as patient survival continues to improve