

Radiotherapy in Neurospecialties

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GENERAL PRINCIPLES OF RADIOTHERAPY → see p. 1711 (1-2) >>

PATHOPHYSIOLOGY

Mitotically active cells are most prone to radiation injury!

- tumor cells are often deficient in *repair mechanisms* (vs. normal cells); **fractionation** (daily small doses of radiation) allows normal cells to repair while tumor cells are unable to do so.
- poorly oxygenated cells** (make up significant proportion of many solid tumors) are 2-3 times less sensitive to radiation than well-oxygenated cells (**oxygen is most powerful radiation sensitizer**); unsuccessful attempts to address this problem:
 - hyperbaric oxygen
 - hypoxic cell sensitizers (e.g. **METRONIDAZOLE, MISONIDAZOLE**)
 - use of neutrons (less dependence on oxygen)
- other radiosensitizers (also not useful) – **IODODEOXYURIDINE, BROMODEOXYURIDINE** – incorporated into DNA of dividing cells (instead of thymidine) – cells become > 3 times more radiosensitive.

Tumor growth is controlled by 2 main mechanisms:

- In higher-dose CENTRAL REGION - **direct cellular injury** (necrosis).
- In lower-dose PERIPHERAL REGION - **vascular occlusion** → fibrosis.

BRAIN TOLERANCE

- depends on:
 - fraction** dose
 - total** dose
 - volume of brain** irradiated
 - age** (children < 3 years are more susceptible than adults).
- risk of injury may be amplified by some **chemotherapeutic agents**.
 e.g. high-dose **methotrexate** with radiotherapy, whether synchronously or at separate times → **necrotizing leukoencephalopathy** (focal areas of coagulative necrosis within white matter).
- vasculopathies** (e.g. **diabetes mellitus**) increase risk of injury.
- threshold doses for brain injury**: 35 Gy for 10 fractions, 60 Gy for 35 fractions, 76 Gy for 60 fractions.

SPINAL CORD TOLERANCE

- 45 Gy in 22 fractions over 5 weeks – safe (0.2% risk of myelopathy).
- tolerance increases with **decreasing fraction size**.
- cervical** and **thoracic** cords do not differ in radiosensitivity (formerly, was belief that cervical cord is more tolerant than thoracic cord).

EXTERNAL BEAM RADIATION THERAPY (EBRT)

- γ-photons** emitted from ⁶⁰Co sources
 - X-rays** generated from linear accelerators
 - particulate radiation (such as **neutrons**) generated from cyclotrons - no therapeutic advantage over X-rays.
- all forms act similarly** - produce fast-moving electrons and free radicals in biologic tissue that **interrupt chemical bonds between DNA base pairs**.
 - disadvantages of traditional EBRT**:
 - loss of function of adjacent healthy tissues.
 - radioresistant tumors (because of dose limitations of surrounding tissues), e.g. **MENINGIOMAS, ACOUSTIC NEUROMAS**.

VOLUMES

Gross tumor volume (GTV) - all known disease, including adjacent nodes, **visible on CT / MRI**.

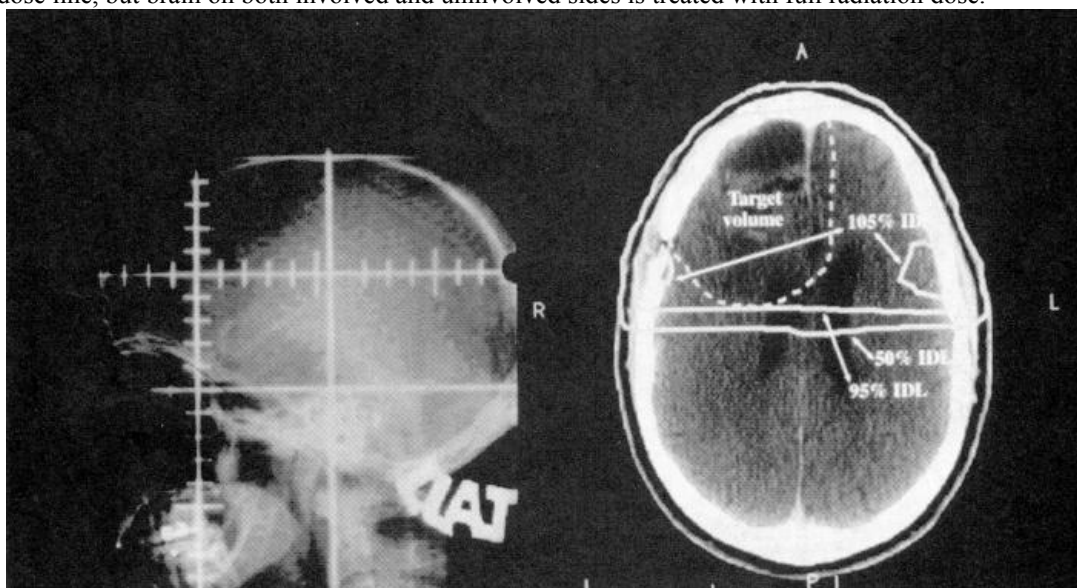
Clinical tumor volume (CTV) - GTV plus surrounding tissue that presumably harbors **microscopic disease**; CTV size depends on tumor histology. see p. Onc3 >>

Planning target volume (PTV) - provides **margin around CTV** to allow for movement and treatment setup variation.

- beam is delivered through **COLLIMATOR**, which shapes beam (i.e. field or treatment area is defined by size and shape of collimator); usually 2-3 portals or fields are used.
- variation in beam intensity, location, angle, shielding can be used to protect surrounding tissue, but, in general, **entire field receives treatment dose** (because healthy tissues are more resistant to effects of radiation, tumor cells are killed while surrounding tissue eventually recovers).
- for target volumes less than whole brain, use **technique sparing surrounding uninvolved normal tissues**:
 - lateral opposed fields
 - wedged pairs
 - three or four field arrangements
 - arcs or full 360° rotations
 - "conformal therapy" - multiple beams with individual beam shaping and intensity.
- treatment mandates **precision in daily setups** - patients are treated **prone, in immobilization cast**; sedation or anesthesia is usually necessary only for youngest children (< 3 yrs).
 - immobilization is especially important in **whole CNS irradiation** - to maintain fixed relationship at junction between lateral opposed fields (used to treat brain) and posterior field (used to treat spinal axis).

Standard partial brain field for frontal lobe glioma;

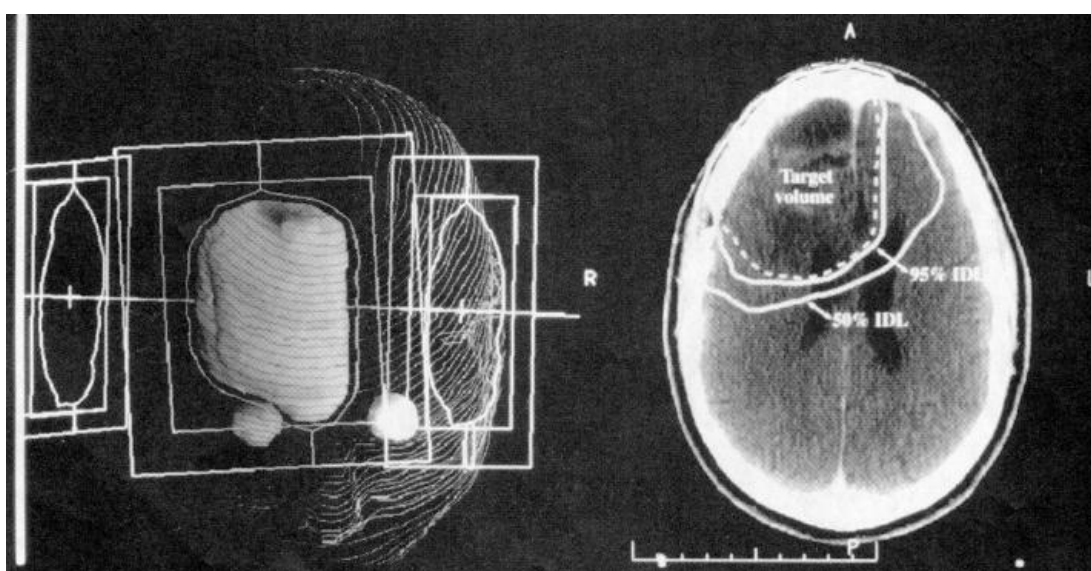
left - simulator film: hatched lines represent 1-cm scale; center of this 11 × 10-cm field is located where hatched lines meet.
right - dose distribution using parallel opposed portals (left lateral and right lateral) - target volume is well encompassed by 95% isodose line, but brain on both involved and uninvolved sides is treated with full radiation dose.



Conformal radiotherapy of same frontal lobe glioma;

left - beam's-eye view of vertex field that is shaped to treat target while avoiding most of normal brain; two smaller round structures inferior to target volume are eyes of patient.

right - dose distribution now conforms much more closely to shape of target volume; normal brain is receiving only 50% of dose.



DOSAGE

- total dose** depends on *tumor histopathology* and on *CNS tolerance*. see p. Onc3 >>

Standard for gliomas – 60 Gy

- small daily fractions are safer and more effective than larger fractions over shorter periods.
- alternative methods** (not more effective clinically):

HYPERFRACTIONATION* (≥ 2 small doses during day) - if sufficient time is allowed between fractions (6-8 hours) for repair of sublethal radiation damage in normal tissues, it is theoretically possible to increase total radiation dose by 25-30% without increasing risk of normal tissue injury.

*does not seem to be worthwhile.

ACCELERATED FRACTIONATION (≥ 2 conventional doses during day - shortened overall treatment time) - reduced opportunity for tumor repopulation (e.g. rapidly proliferating *GLIOBLASTOMA MULTIFORME*).

STEREOTACTIC RADIATION

- delivery of precise dose of high-energy radiation through stereotactically directed multiple, well-collimated beams converging on small lesion.

- sophisticated imaging devices and 3D treatment-planning computers allow **much more specific targeting of lesion** - significantly less radiation to surrounding healthy tissues.
- little additional survival benefit over external-beam radiotherapy.
- RADIATION THERAPY PLANNING** currently takes 2 forms:
 - BEAM FIRST (s. FORWARD) PLANNING** - *target volume* of radiation is determined first, and then surrounding tissue volume is planned; works extremely well in tumors with **regular** or **spherical shape**.
 - DOSE-FIRST (s. INVERSE) PLANNING, s. PEACOCK TOMOTHERAPY** - determines safe *dose for surrounding healthy tissues* first, and then computer workstation determines required beam intensity and shape for each portion of field; works very well for **irregularly shaped** lesions.
- in past, stereotactic radiation could only be delivered in single dose; today, because of **noninvasive fixation devices**, single-treatment delivery is no longer mandatory.

A. STEREOTACTIC RADIOSURGERY (SINGLE-DOSE STEREOTACTIC RADIATION TREATMENT)

- highly focal, closed skull (noninvasive!) external irradiation that uses stereotactic device for precise target localization (high radiation dose* to intracranial target in single session without delivering significant radiation to adjacent normal tissues).

Can achieve tumor ablation without craniotomy!

*even radioresistant tumors can be treated

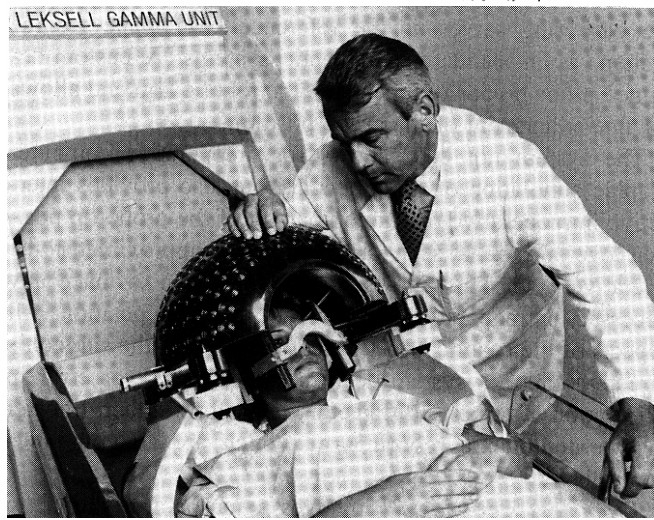
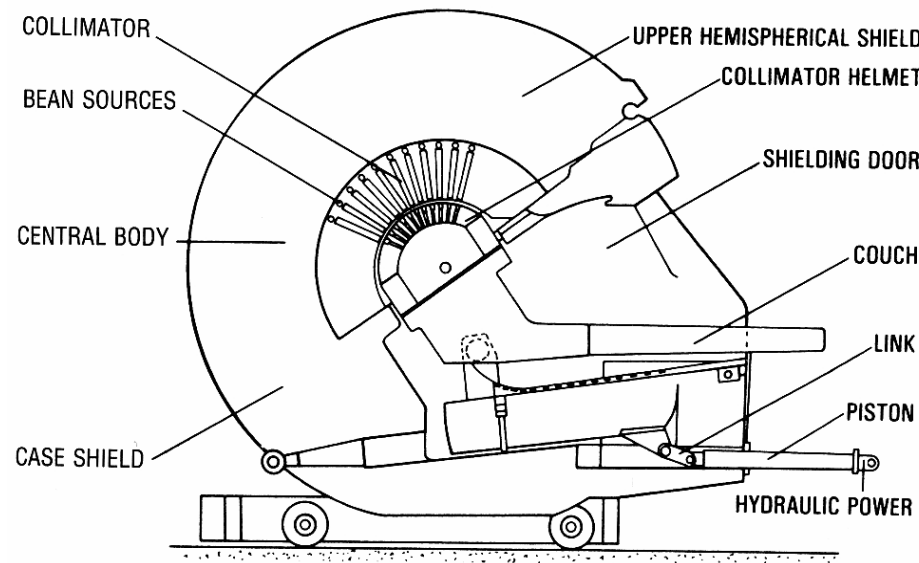
- term formulated by Lars Leksell, MD in 1951.
- used either as boost to conventional, fractionated radiation or as single treatment.
- radiation beams intersect at one point (or sometimes more, called **ISOCENTERS**).
- can be administered by:**
 - “gamma knife”** (multiple highly collimated ^{60}Co beams) – very precise.
 - modified **linear accelerators [LINACs]** (rotational high-energy photon beam) – mechanical accuracy comparable to gamma knife.
- first step in single-dose procedure is to attach patient's head to **stereotactic head frame** (has coordinate system for target determination).
- next, **series of images** are taken with head ring in place (CT, MRI, SPECT, or PET).
- images are transferred with underlying coordinate system to **computer workstation**.
- physician, working on virtual tumor on computer, prescribes *individual treatment plan* by outlining lesion to be treated, using computer mouse in paintbrush fashion.
- final verification is performed with **TARGET POSITIONER** (i.e. trial run is performed on positioner before treating patient).
- because dose that can be safely administered in single fraction is limited by volume irradiated, radiosurgery is **restricted to ≤ 4 cm lesions** (e.g. small AVMs, pituitary adenomas, acoustic neurinomas, meningiomas, small gliomas, small brain metastases).
 - in > 4 cm, irradiation of surrounding structures becomes too great*
 - gliomas, with no well-defined margin, are not ideally treated with radiosurgery.
 - tumor may appear to grow immediately after treatment.
 - treatment can worsen peritumoral edema (H: prolonged course of high-dose steroid).
- may also be used to create anatomical physiological lesions for **pain and movement disorders**.

- **several lesions** can theoretically be treated on single clinic visit (as number of lesions increase, overlapping of fields exceeds tolerance of healthy brain to radiation injury!).

B. FRACTIONATED STEREOTACTIC RADIATION TREATMENT

A. Cross-section of **gamma knife** showing cobalt 60 sources in central body aligned with primary collimators and collimator helmet.

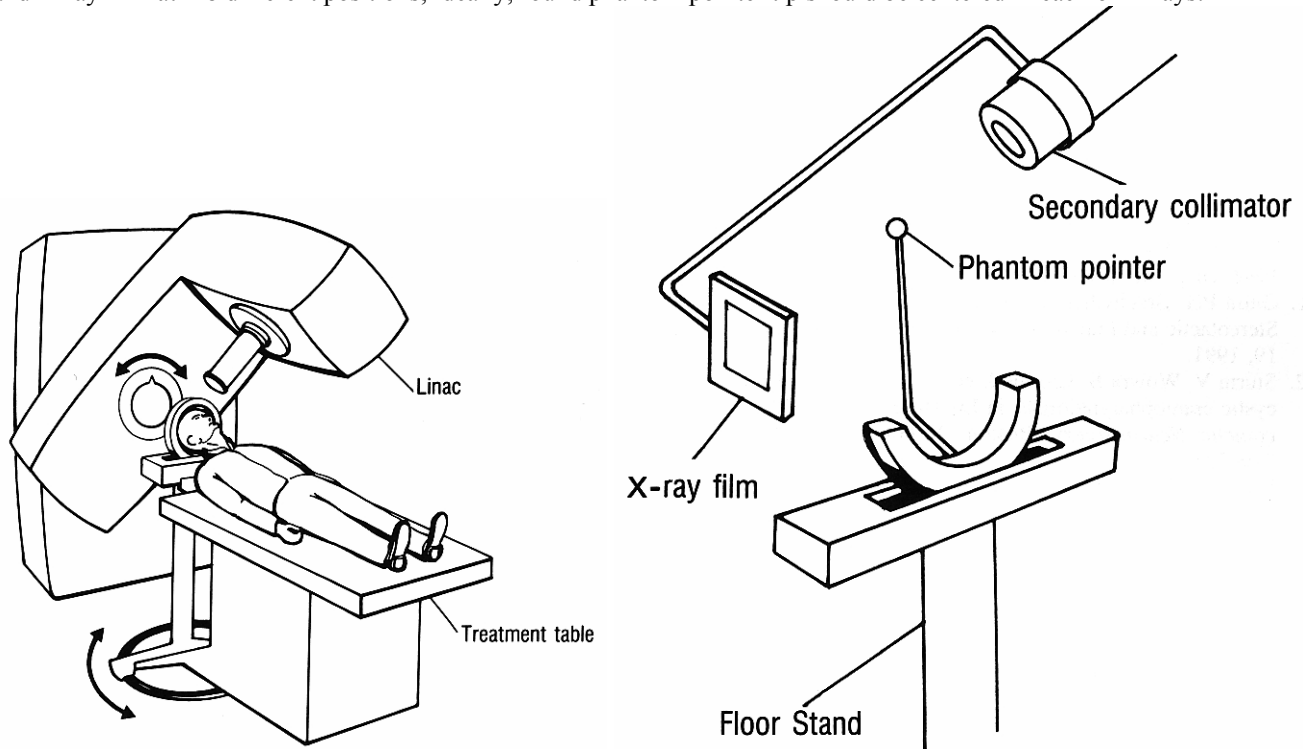
B. Patient is fixed in stereotactic frame with intracranial target centered at isocenter of collimator helmet; shield and shielding door are seen immediately behind patient:



Source of pictures: Marshall B. Allen, Ross H. Miller "Essentials of Neurosurgery: a guide to clinical practice", 1995; McGraw-Hill, Inc.; ISBN-13: 978-0070011168 >>

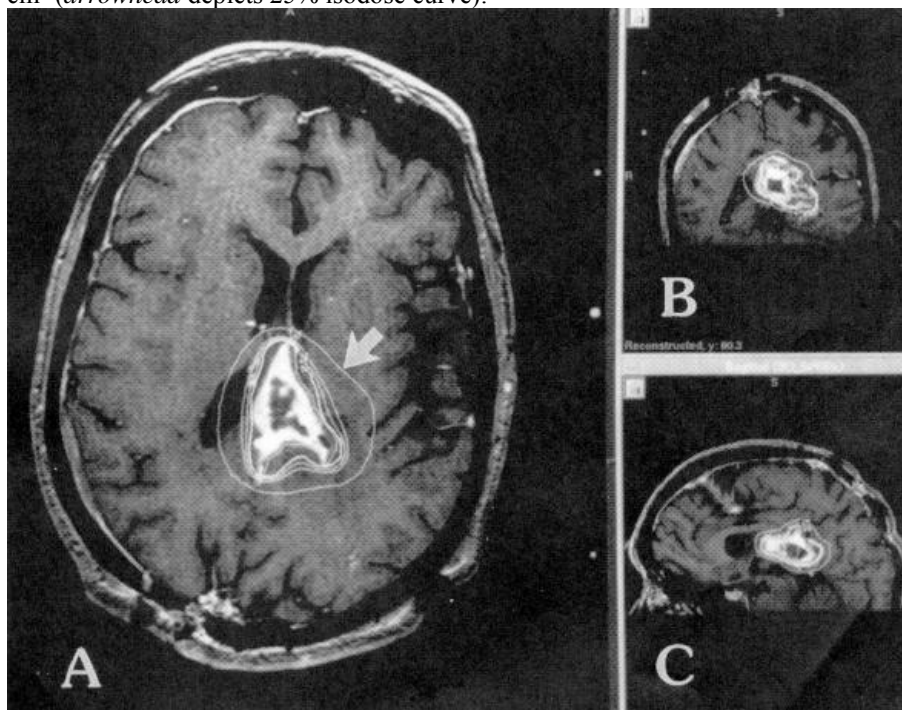
A. **LINAC-based radiosurgery system**; LINAC moves through variable degree treatment arc, usually five more times. With each treatment arc, patient and treatment table are rotated into different position.

B. Many LINAC-based radiosurgery centers perform recollimation before each procedure; this consists of passing X-ray beam from LINAC through phantom pointer fixed at isocenter of stereotactic instrument. X-rays are obtained with LINAC and X-ray film at 4-8 different positions; ideally, round phantom pointer tip should be centered in each of X-rays.



Source of picture: Marshall B. Allen, Ross H. Miller "Essentials of Neurosurgery: a guide to clinical practice", 1995; McGraw-Hill, Inc.; ISBN-13: 978-0070011168 >>

Gamma-knife treatment plan for recurrent glioblastoma multiforme in deep left corpus callosum, thalamus, and parietal region inclusive of atrium of ventricle; superimposed 50, 45, and 25% isodose curves enclose defined target volume of 9.9 cm³ (arrowhead depicts 25% isodose curve):

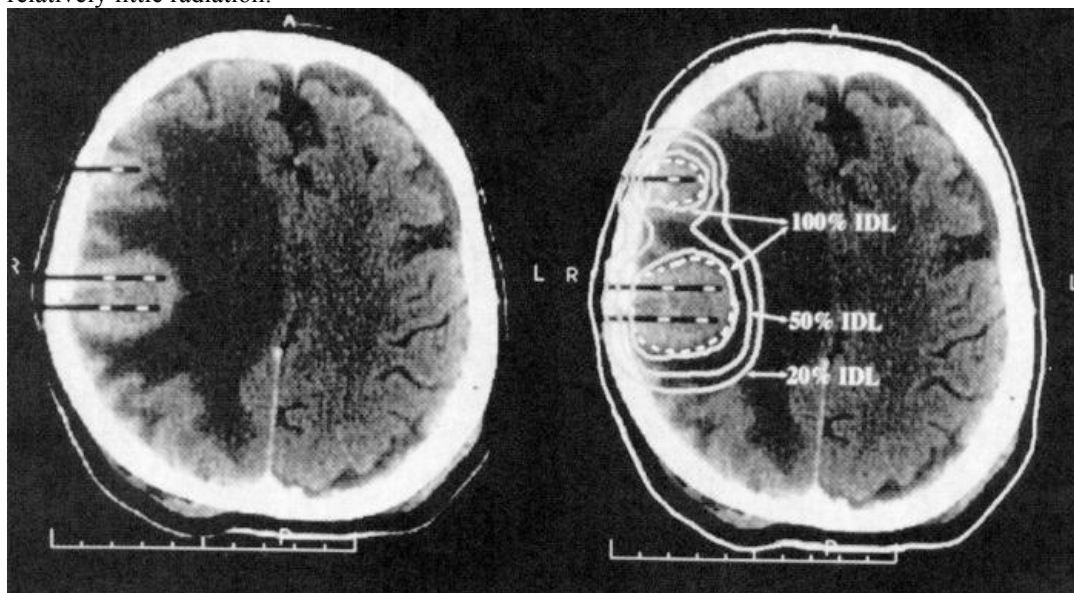


BRACHYTHERAPY (INTERSTITIAL / IMPLANTED RADIATION THERAPY)

- ¹²⁵I₃ or ¹⁹²Ir₄ "seeds" placed by stereotactic techniques.
Invasive! (vs. radiosurgery)
- rapid dose falloff around "seeds" - localized high-dosage (40-120 Gy) radiation with sharp edges and sparing of adjacent brain.
- effectiveness as of radiosurgery.
- **ideal candidate** - unifocal, well-defined, supratentorial tumor < 5 cm* in diameter that does not involve corpus callosum, brain stem, or ependymal surfaces.
*treatment of larger tumors can lead to life-threatening edema
- patient wears **lead-lined helmet** when others enter his private room.
- **steroids** are given during the period of treatment (to prevent surrounding reactive edema).

- typically, sources (along with stereotactically placed afterloading catheters) are removed after 5-6 days of treatment.
- high incidence of **radiation necrosis!**

Stereotactic implant of bilobed brain tumor - hollow catheters placed inside tumor-bearing region; radioactive seeds are then loaded into catheters; dose distribution is extremely tight around target volume and remainder of normal brain receives relatively little radiation.



RADIOCOLLOIDAL SOLUTIONS

- placed **into cystic cavities** (to control fluid reaccumulation, to decrease cystic tumors and consolidate their capsule → safer surgery):

- ^{90}Y - maximum range of β particles is 8 mm; > 50% dose absorbed by first 1.1-1.5 mm of tissue.
 - ^{32}P - half-value layer penetration 0.8 mm - lower risk of injury to surrounding vascular / neural structures.
 - ^{186}Re
 - ^{198}Au
- no significant radiation dose to associated solid tumor components.
 - suspension is aspirated after several days.

SIDE EFFECTS

Most patients tolerate radiotherapy remarkably well (worsening of neurologic status during treatment is unusual).

- 1) mild skin **erythema** may be seen in first week of treatment.
 - moist desquamation may occur in retroauricular region where skin sparing is lost.
 - **topical steroid creams** are adequate (if treatment is necessary).
- 2) temporary **alopecia** within radiotherapy fields is universal; women usually have return of hair growth after treatment; hair growth in men is more variable.
 - if skin dose is excessive (e.g. over frontal region, vertex, and occiput, where radiation beam enters tangentially and so loses skin-sparing properties of perpendicular beam), permanent alopecia may occur.
- 3) **otitis media / externa** - after radiotherapy to posterior fossa (eustachian tube is obstructed by swelling).
- 4) **fatigue** - occurs toward end of radiotherapy; can persist for several weeks.
- 5) some degree of **hematologic suppression** is seen with treatment to *whole CNS*.

COMPLICATIONS

- reported as infrequent (2-5% cases) - unrealistically low - reflect fact that most irradiated patients with tumor die before brain injury appears.

- mechanism of injury - **peroxidation of lipids** in myelin and neuronal membranes (DNA synthesis, primary target of radiation, occurs infrequently in neurons).
- severity depends on individual BRAIN TOLERANCE. *see above >>*

CORTICOSTEROIDS may improve neurologic symptoms associated with radiation injury (at least in ACUTE and EARLY-DELAYED reactions)

ACUTE REACTIONS

(occur during or shortly after irradiation up to 6 weeks) - caused by **radiation-induced edema** → **acute encephalopathy**:

- most common after **large dose fractions** (3.0-6.0 Gy) delivered to large brain volume: within few hours after first fraction - headache, nausea, vomiting, somnolence, fever, and worsening neurologic symptoms (if ≥ 7.5 Gy are used, may culminate in death).
- with **conventional daily fractions** (1.8-2.0 Gy) - mild headache and nausea, becoming progressively **less severe with each succeeding fraction**.
- prophylaxis & treatment - start **corticosteroids** for at least 48-72 hours before radiotherapy (dose can usually be tapered relatively early, and often discontinued after 1-2 weeks).

EARLY-DELAYED REACTIONS

(appear within 1-6 months after irradiation) - **temporary demyelination** caused by:

- a) radiation effect on **oligodendroglial cells** → demyelination.
- b) radiation-induced changes in **capillary permeability** (i.e. transient disruption of BBB) → vasogenic edema → demyelination.

Transient radiation leukoencephalopathy - neurologic deterioration (e.g. reappearance of initial tumor's symptomatology), focal encephalopathy, "**somnolence syndrome**" in children (lethargy, anorexia, headache, ataxia - last \approx 1-2 weeks).

- resolves within several weeks without specific sequelae.
- **CT** – hypodensity of white matter.
- **EEG** – diffuse slow-wave activity.
- prophylaxis & treatment - **corticosteroids**

Transient radiation myelopathy - develops after latent period of 2-4 months → gradually resolves over ensuing 3-6 months without specific therapy!

- momentary, electrical shock-like paresthesias / numbness radiating from neck to extremities, precipitated by neck flexion (**Lhermitte's sign**).

LATE-DELAYED REACTIONS

(develop > 6 months after irradiation) – permanent damage:

Secondary neoplasia – meningiomas (!!!), soft tissue sarcomas, nerve sheath tumors, thyroid cancers (after treatment to spinal axis).

Hypothalamic-pituitary suppression - dose related (esp. *GROWTH HORMONE deficiency* - can occur after doses as low as 18 Gy; *TTH* is least sensitive).

- yearly endocrine evaluations should be done for at least first 3 years after therapy.
- early detection of deficiency permits appropriate hormonal replacement therapy before irreversible damage has occurred.
- spinal radiotherapy may cause **growth arrest** in children.

Radiation necrosis - most serious consequence of standard radiotherapy (single most dose-limiting factor) - idiosyncratic coagulative *white matter necrosis* caused by:

- VASCULAR HYPOTHESIS: vascular **endothelial** injury → hyalinized thickening of blood vessels → thrombosis & occlusion of capillaries and small arteries.
- GLIAL HYPOTHESIS: direct effect on **oligodendroglial** cells.
- IMMUNOLOGIC HYPOTHESIS: irradiated glial cells release antigens that induce **autoimmune** reaction.

- develops with increasing frequency with increasing radiation doses (e.g. only < 1% patients treated with conventional dose-fractionation).
- onset 6 months ÷ 10 years after treatment.
- *asymptomatic ÷ potentially fatal*.

A) **RADIATION NECROSIS** (after *localized therapy*) - focal lesion at original tumor site.

- **clinically** - acts as **expanding mass lesion**: focal neurologic signs (re-emergence of initial tumor symptoms), seizures, increased ICP (can be fatal via herniation).
- **imaging** - **contrast-enhancing mass surrounded by vasogenic edema**.
- radiation necrosis induces **clinical** and **CT/MRI** changes indistinguishable from tumor progression – can be differentiated with **DYNAMIC TESTING**: see p. Onc1 >>

Radiation necrosis is hypometabolic, tumor is hypermetabolic

- 1) **perfusion-weighted MRI**
- 2) **MRS**
- 3) **PET** using ¹⁸fluoro-deoxyglucose
- 4) **SPECT**

N.B. because most patients have mixture of necrosis and tumor, **biopsy** may be required to confirm diagnosis! (also often ameliorates symptoms)

- biopsy sample must be only large enough to exclude tumor recurrence without causing clinically significant neurologic deficits.
- *histologic hallmark of radiation necrosis* - demyelination and oligodendrocyte dropout; necrotic tissue without predominance of malignant cells.

MRI signs suggesting necrosis (vs. tumor):

- 1) nonenhancing tumors prior to surgery.
- 2) lesion some distance from primary glioma but within radiation field.
- 3) lesion in periventricular white matter.
- 4) lesion has soap-bubble or Swiss-cheese appearance.

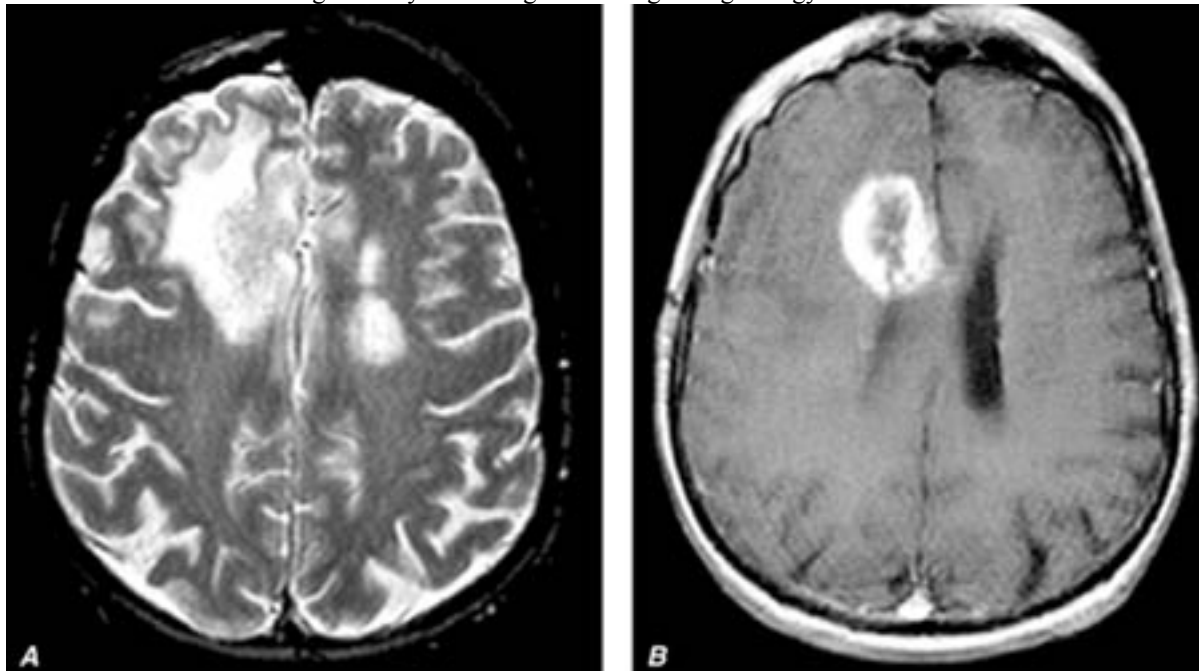
• treatment (in addition to **steroids**):

- observation** – for asymptomatic cases.
- surgical debulking** – for favorably situated symptomatic lesions.
- anticoagulation** (alternative when surgery is not feasible; **HEPARIN** to aPTT↑ 1,5 times control) – because radiation necrosis pathophysiology involves vessel thrombosis and subsequent occlusion; lacks demonstration of real benefit.
- hyperbaric oxygen therapy** (20-24 atm. for 20-30 sessions 90-120 minutes each) – promotes perfusion and angiogenesis; efficacy is not well documented.

Focal radiation necrosis 3 years after radiotherapy (70 Gy) for nasopharynx carcinoma:

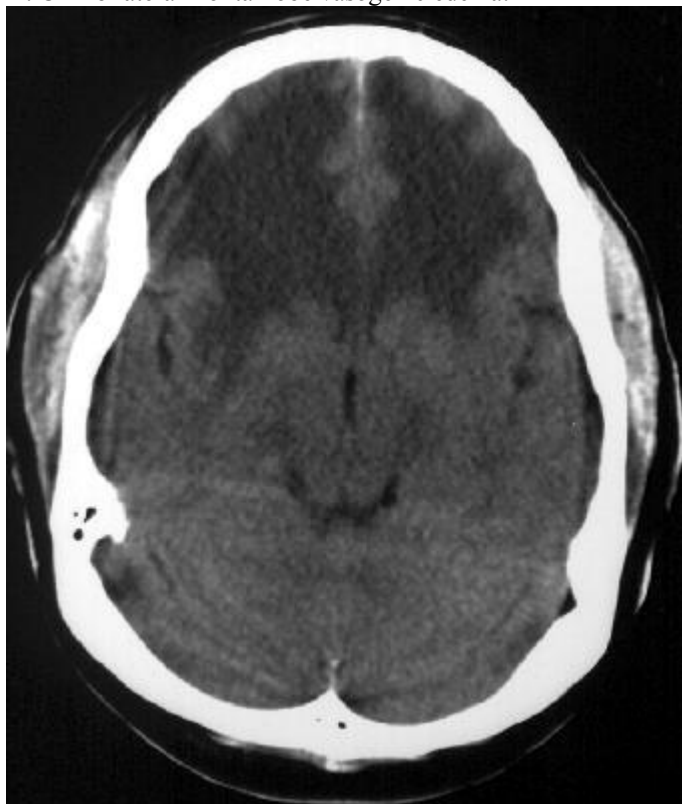
A. T2-MRI - mass in right frontal lobe with surrounding vasogenic edema; abnormal signal also on left.

B. Contrast T1-MRI - heterogeneously enhancing mass in right cingulate gyrus.

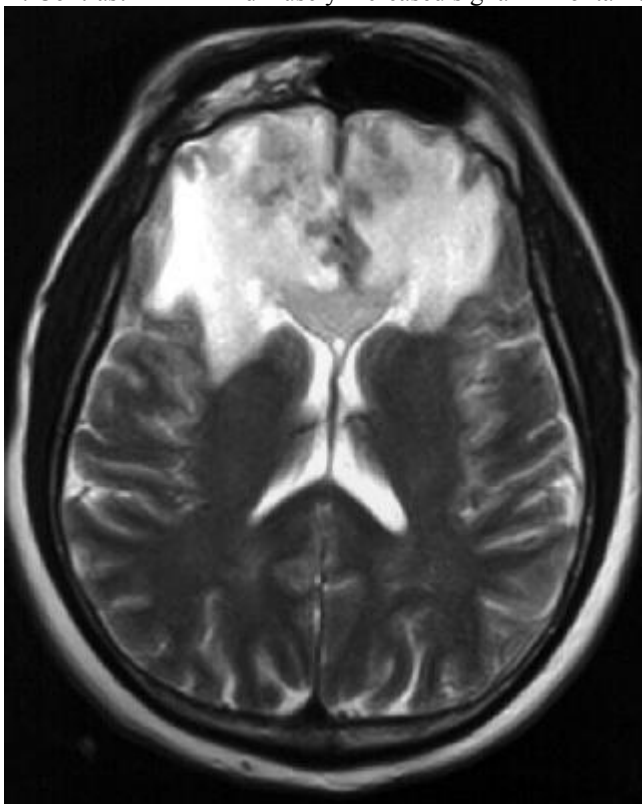


Other example (after radiotherapy for maxillary sinus carcinoma):

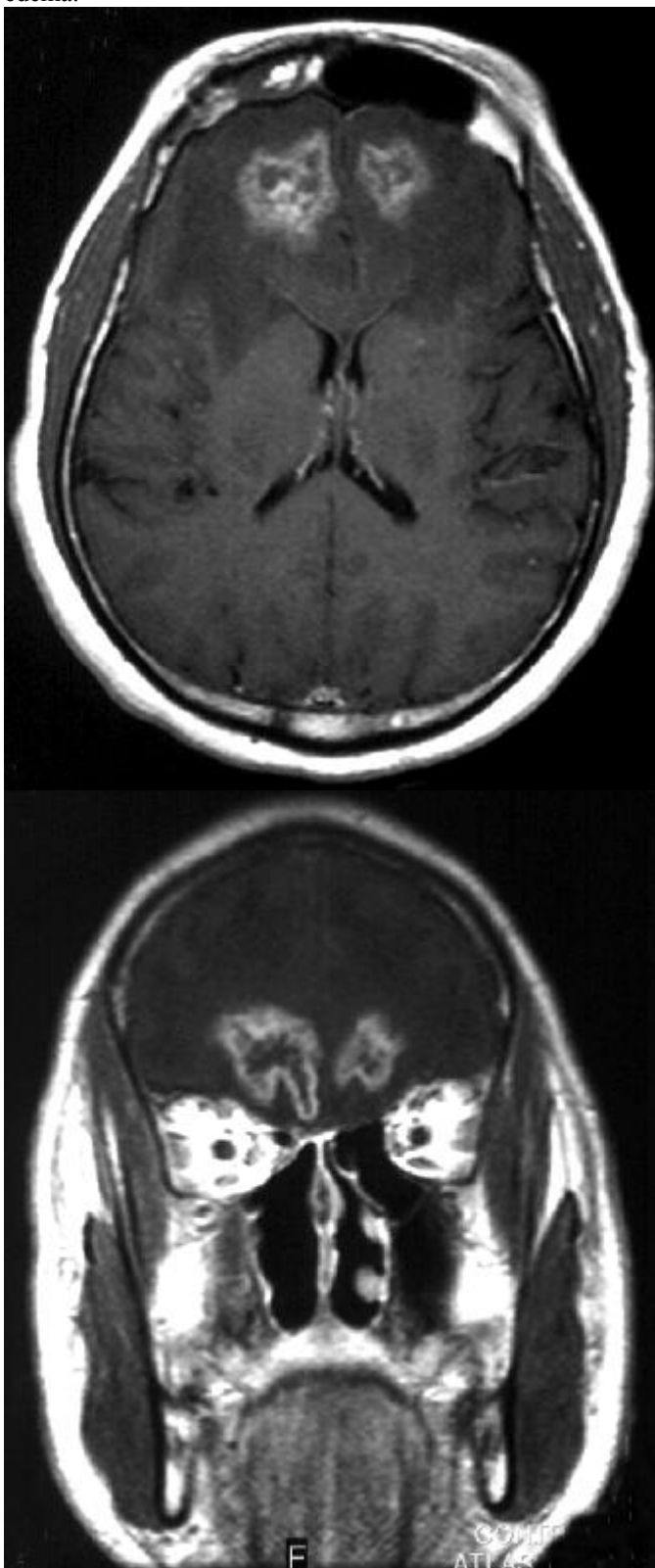
A. CT - bilateral frontal lobe vasogenic edema:



B. Contrast T2-MRI - diffusely increased signal in frontal lobes:



Contrast T1-MRI - two lesions in frontal lobes bilaterally; rim enhancement; decreased surrounding signal is edema:



B) DIFFUSE WHITE MATTER INJURY (after *whole-brain radiation*) - varying degrees of **neuropsychological impairment** (up to incapacitating dementia), **gait apraxia**.

- CT **diffuse white matter hypodensity** (atrophic dilatation of adjacent ventricle indicates demyelination rather than edema).
- MRI-T2 **diffuse nonenhancing periventricular white matter hyperintensity**.
periventricular white matter is highly susceptible to radiation injury!
- **diffuse cerebral cortical atrophy** (late finding related to diffuse white matter injury) is observed in 17-39% patients.

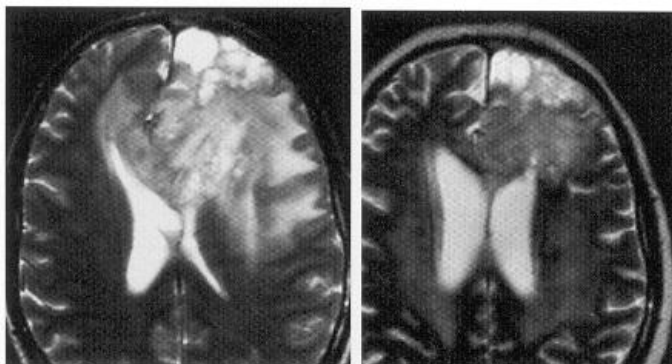
Dementia ($\geq 50\%$ patients who survive whole-brain radiation for 5 years).

- becomes fully developed after several years.
- most pronounced in patients who have had whole-brain irradiation + chemotherapy.
- local field (vs. whole-brain) radiation has reduced incidence of dementia.
- **special problem in children** - irradiated children have IQ decrements and behavioral disturbances; even radiation fields limited to posterior fossa have been associated with intellectual declines! - yearly psychologic evaluations should be done for at least first 3 years after therapy.
- **MRI / CT** - cerebral atrophy.

Anaplastic astrocytoma (MRI-T2):

A. Before treatment - large mixed solid and cystic tumour in left frontal lobe which infiltrates across corpus callosum and causes considerable mass effect; vasogenic edema lateral to tumor.

B. After treatment - tumour has shrunk with regression of mass effect and edema; subtle diffuse high signal separate from tumor in white matter of both cerebral hemispheres (radiation-induced leukoencephalopathy).



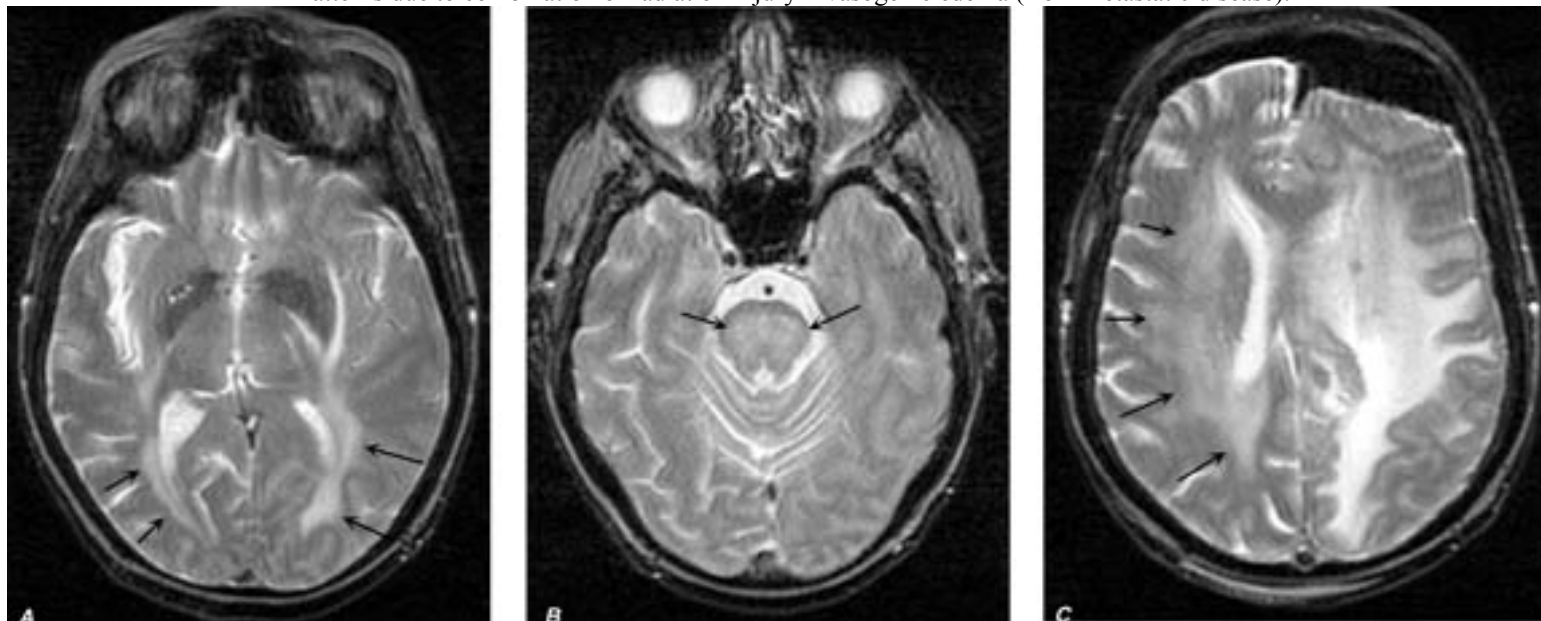
A Source of picture: Ronald G. Grainger, David J. Allison "Grainger & Allison's Diagnostic Radiology: A Textbook of Medical Imaging", 4th ed. (2001); Churchill Livingstone, Inc.; ISBN: 978-0443064326 >>

T2-MRI of **diffuse white matter injury** 1 year following whole-brain radiation (55 Gy):

A. High signal in periventricular white matter (*arrows*).

B. Diffuse high signal in pontine white matter (*arrows*) - demyelination or small vessel ischemic injury.

C. Radiation injury to white matter of right hemisphere (*arrows*); in left hemisphere higher signal of white matter is due to combination of radiation injury + vasogenic edema (from metastatic disease).



Radiation Myelopathy – irreversible! - one of most feared complications in clinical radiotherapy!

- **pathophysiology** – as in radiation necrosis of brain (i.e. spinal cord infarction with necrosis, hemorrhage, and demyelination).
- bimodal distribution - first peak at 12-14 months after irradiation and second at 24-28 months.
- **incidence** for conventionally fractionated irradiation (1.8-2 Gy per fraction, 5 fractions per week): 57-61 Gy - incidence 5%; 68-73 Gy - incidence 50%.
- **clinical features**:
 - insidious onset: painless progressive paresthesias, UMN & LMN weakness that may progress (over several months) to complete paraplegia.
 - rarely, abrupt onset – due to infarction.
- **diagnosis** - no confirmatory imaging / laboratory studies (diagnosis of exclusion); **MRI / myelography** - to rule out compressive lesion.
 - T2-MRI – slightly swollen cord with signal↑ regions → myelomalacia.
 - T1-MRI – vertebral marrow replacement with fatty tissue (homogeneously bright vertebrae).
- no known **treatment** (steroids may improve symptoms transiently).
- ≈ 50% patients die from secondary complications.

Radiation-Induced Vasculopathy

- latent period can be up to 23 years.
- typically affects extra- or intracranial portions of **INTERNAL CAROTID ARTERIES**.
- **accelerated atherosclerosis**, localized stenosis, irregular vessel contour, even complete occlusion of portion of artery in radiation portal.
- **moyamoya pattern** may develop.
- **telangiectatic vessels** (may hemorrhage) occasionally form.
- **mineralizing microangiopathy** with dystrophic calcification - punctate calcifications in basal ganglia, cortex and brain stem; asymptomatic.
- **clinically**: TIA, ischemic stroke.

Radiation Optic Neuropathy

- develops within 3 yrs after treatment directed to orbit, sinuses, pituitary, or intracranial tumors.
- **painless visual loss** (usually monocular), papilledema in most (→ optic atrophy later), hemorrhagic exudates.
- 50% patients improve, some become blind.
- T2-MRI - high signal in intracranial portion of optic nerve.
- **steroids** are ineffective.
- **prophylaxis** - **shield optic nerve** from radiation portals.

Radiation-Induced Neuropathy (incl. radiculopathies, plexopathies)

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