Radiation Therapy for Primary Brain Tumors

Luke R.G. Pike MD DPhil
Director of CNS Radiation Oncology
Memorial Sloan Kettering Cancer Center

Epidemiology

- 22,500 primary malignant brain tumors per year
- Malignant gliomas account for ~75-80%
  - Glioblastoma (50-60%)
  - Anaplastic astrocytomas (10-15%)
  - Anaplastic oligodendrogliomas/mixed (10%)
  - Anaplastic ependymoma/gangliogliomas
- Median age @ diagnosis for GBM = 64 years
- Slight male predominance

Etiology and Genetics

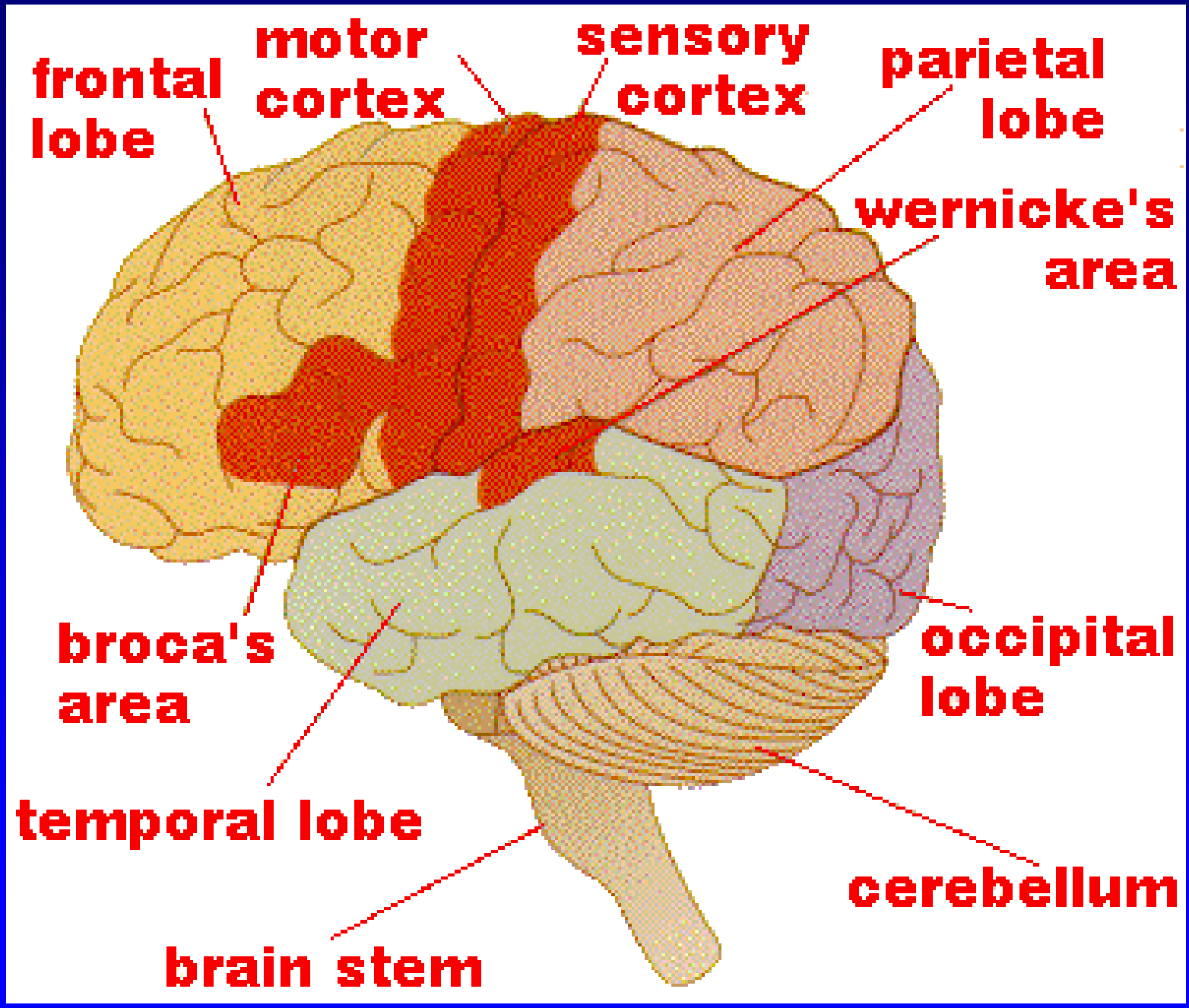
- Most brain tumors are sporadic
- Inheritable disorder or syndromes
  - Turcot syndrome (colonic adenomatous polyposis, medulloblastoma, and malignant glioma)
  - Tuberous Sclerosis
  - neurofibromatosis type 1 (increased prevalence of many tumors, including all grades of glioma and breast cancer)
  - Li-Fraumeni syndrome (breast, soft tissues sarcoma, leukemia, and brain malignancies). -- P53 mutation

Etiology and Genetics

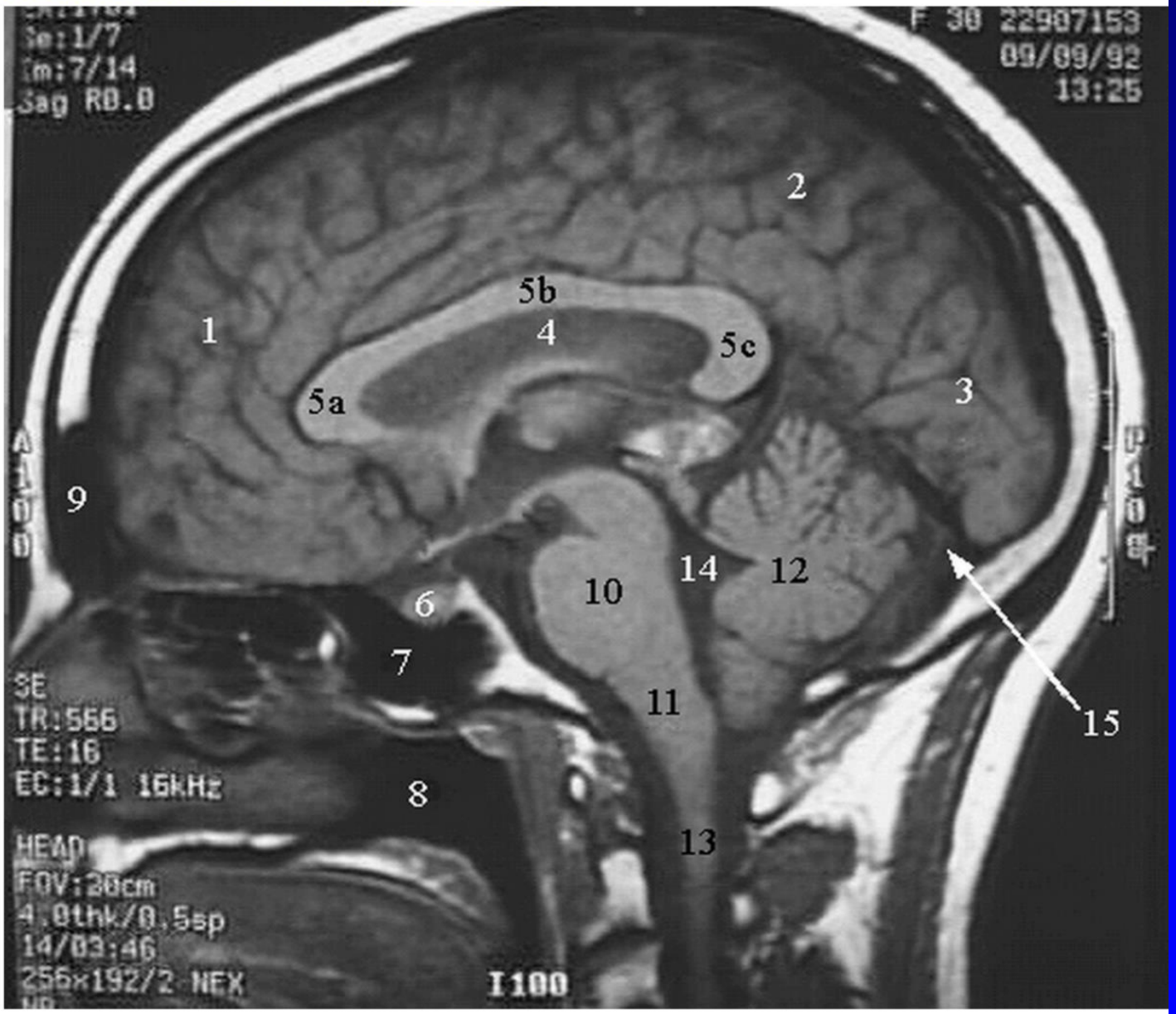
- mutation of p53 in 40% of GBM
- The overexpression of epidermal growth factor receptor appears to occur in the absence of p53 mutations in 90% of GBMs that are clinically considered likely to be primary
- environmental mutagens such as radiation and certain chemical substances, such as vinyl chlorides

Presentation

- Headache (increased ICP)
- Nausea/Vomiting (increased ICP)
- Seizure (low grade tumor)
- Focal Neurologic Deficit


frontal lobe
motor cortex
sensory cortex
parietal lobe
wernicke's area
broca's area
occipital lobe
temporal lobe
cerebellum
brain stem

Head & Neck: Head MRI Midline:



Head & Neck: Head MRI Midline:



1. Frontal Lobe.
2. Parietal Lobe.
3. Occipital Lobe.
4. Septum Pellucidum.
5. a. Rostrum of Corpus Callosum.
   b. Body of Corpus Callosum.
   c. Splenium of Corpus Callosum.
6. Pituitry.
7. Sphenoid air sinus.
8. Nasopharynx.
9. Frontal Air sinus.
10. Pons.
11. Medulla Oblongata.
12. Cerebellum.
13. Spinal Cord.
14. Fourth ventricle.
15. Sinus Confluence.

Types of Primary Brain Tumors

- **Meningiomas** (50% of primary CNS tumors) often operable and benign.
- **Gliomas**
  - Glial cells (40% of CNS tumors) give rise to specific tumor types include astrocytes (astrocytomas), oligodendrocytes (oligodendrogliomas), and ependymal cells (ependymomas).
  - Oligodendrogliomas (10%) arise from oligodendrocytes, less aggressive, more responsive to chemo/rt, typically cortically based,exhibit los of 1p and 19q13 uitor 9q and 22.
- Ependymomas arise from ependymal cells lining ventricles, can block CSF flow resulting in hydrocephalus
- Gangliogliomas are discrete low-grade tumors containing both neurons and glial cells. High rate of cure with surgery alone or surgery with RT.
- Schwannomas arise from schwann cells surrounding cranial nerves usually involving VIII (acoustic neuroma)
- Neuronal cells form specific tumors depending on location. Transformation of neuroblasts in the cortex (cortical PNETs), retinal neuroblast(retinoblastoma), and pineal gland neuroblasts (pineoblastomas).
- Other specialized tumors pituitary gland (pituitary adenomas), pineal gland (pineocytomas), notochord remnants (chordomas), endothelial cells (hemangioblastomas), primitive germ cells (germ cell tumors), and choroidal epithelial cells (choroid plexus papillomas).

Gliomas WHO Classification

Grade	Designation
I	pilocytic astrocytoma
II	diffuse astrocytoma
III	anaplastic astrocytoma
IV	glioblastoma multiforme

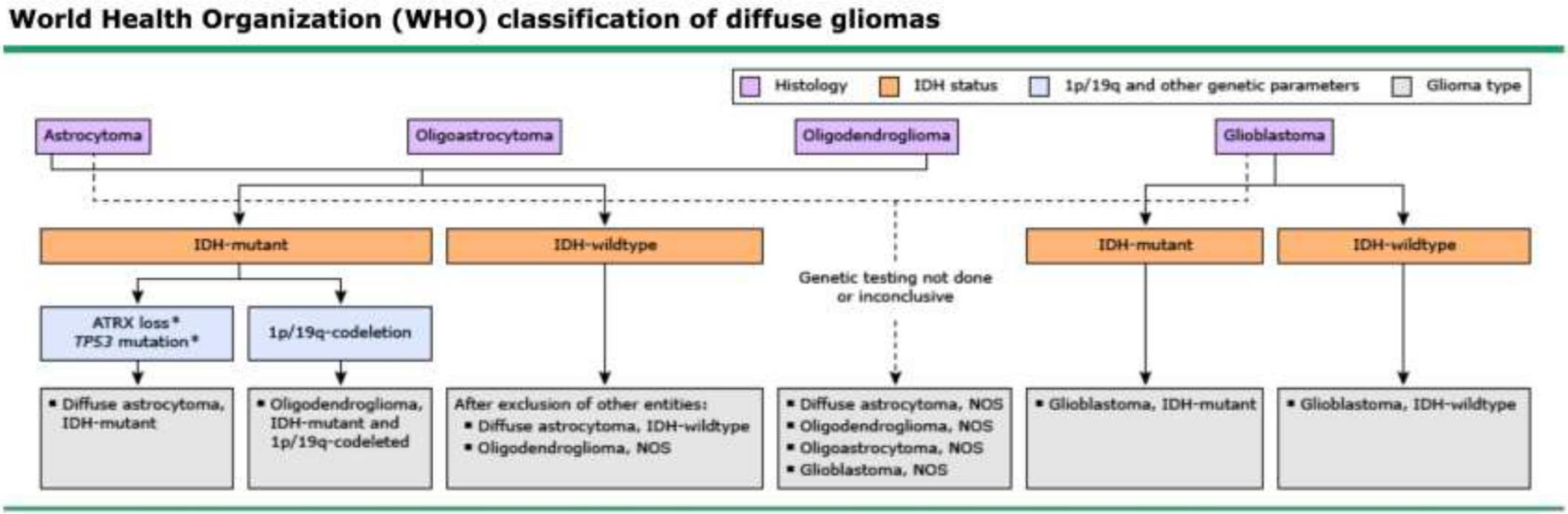
"Low-grade" = WHO grade I, II

"High-grade" = WHO grade III, IV

WHO II Criteria

- Grade 1. **Circumscribed astrocytoma**. Generally benign, well circumscribed astrocytic tumor. Most common example is a juvenile pilocytic astrocytoma
- Grade 2. **Astrocytoma**. Diffusely infiltrating, well differentiated astrocytes with minimal pleomorphism or nuclear atypia, no vascular proliferation or necrosis
- Grade 3. **Anaplastic astrocytoma**. Vascular proliferation and necrosis are absent, increased cellularity, pleomorphism and nuclear atypia, mitotic activity
- Grade 4. **Glioblastoma multiforme**. Increased cellularity, anaplasia and pleomorphism, cell type may be poorly differentiated, fusiform, round or multinucleated, prominent vascular proliferation or necrosis, variable mitotic activity.

WHO 2016 Molecular Classification



Malignant Brain Tumors

- Low grade glioma
  - Pilocytic astrocytomas (grade 1)
  - Oligodendrogliomas (grade 2, IDH mut, 1p19q codel)
- High grade glioma
  - Anaplastic gliomas (grade 3, IDH mut, 1p19q intact)
  - Glioblastoma (grade 4, IDH WT)

Low Grade Glioma

- Pilocytic astrocytoma (WHO I)
  - Occur in children age 5-14 years: juvenile pilocytic astrocytoma
  - These tumors are usually discrete, indolent lesions associated with cyst formation. The cysts can be unilocular or multilocular, with an associated tumor nodule.
  - Cerebellar JPA
    - Most common site of occurrence
    - Surgery is primary treatment for cerebellar and cerebral JPA
      - After GTR, 10 yr OS approaches 100%
      - Even after STR, withhold XRT for recurrence
  - Optic Pathway Gliomas (most commonly JPA)
  - Optic gliomas (60% of which are pilocytic astrocytoma) are associated with neurofibromatosis type 1 (NF1). Patients with optic pilocytic astrocytomas associated with NF1 usually have better outcomes than those of other patients with juvenile pilocytic astrocytomas because the tumor is more likely to be confined to the optic nerve. Bilateral optic gliomas are more common in patients with NF1.

Low Grade Glioma

- Oligodendroglioma
  - Grade 2 tumors
  - Usually IDH mutant and 1p19q codeleted
  - More common in younger adults ~40yo

High Grade Glioma

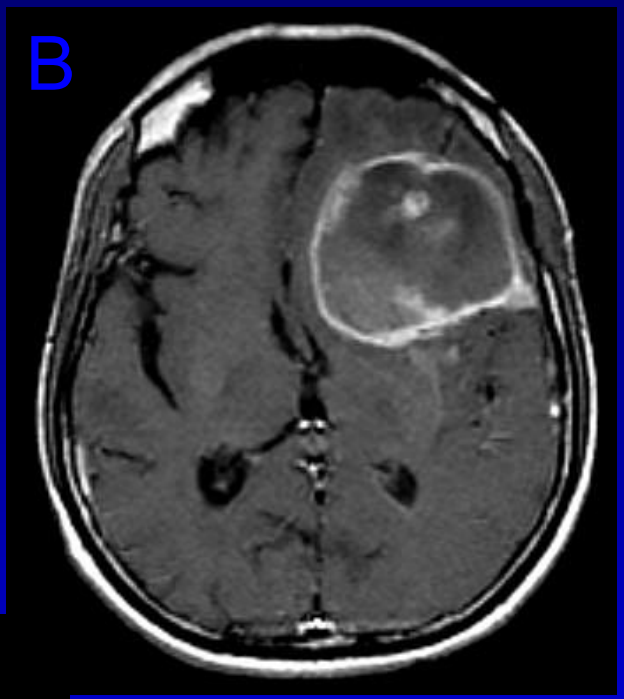
- **Anaplastic Astrocytoma WHO III**
  - Peak incidence at 50 yrs
  - Pathology: nuclear atypia and mitotic activity (distinguishes from WHO II)
- **Glioblastoma multiforme (GBM) WHO IV**
  - 25% of all brain tumors, peak incidence > 50 yrs.
  - Pathology: nuclear atypia, mitotic activity, endothelial proliferation and necrosis.
  - GBM's arise most commonly de novo (**1^{ary} GBM**).
  - Some GBM's arise by malignant transformation of low-grade astrocytomas (**2^{ary} GBM**).
  - Primary GBMs are more common in older patients and are more aggressive.

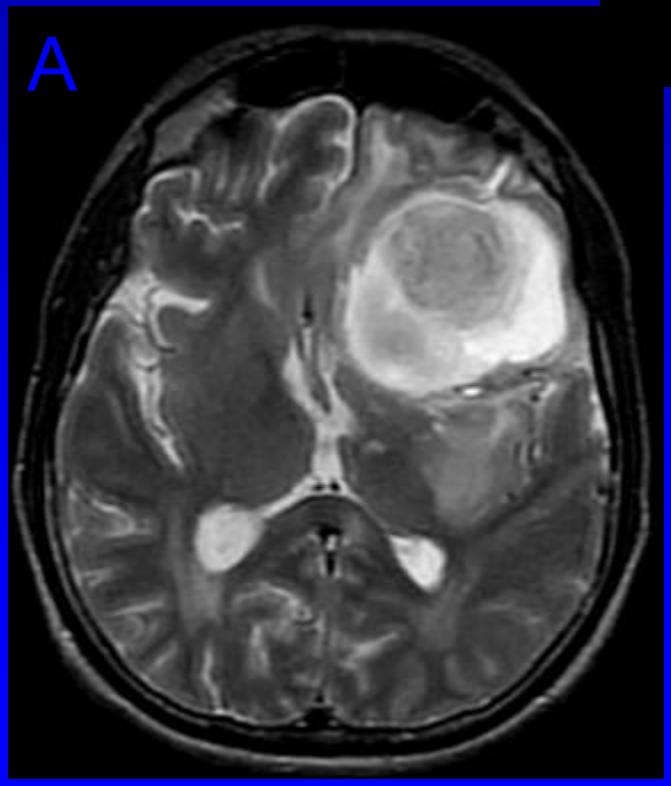
Cheat Sheet for Gliomas

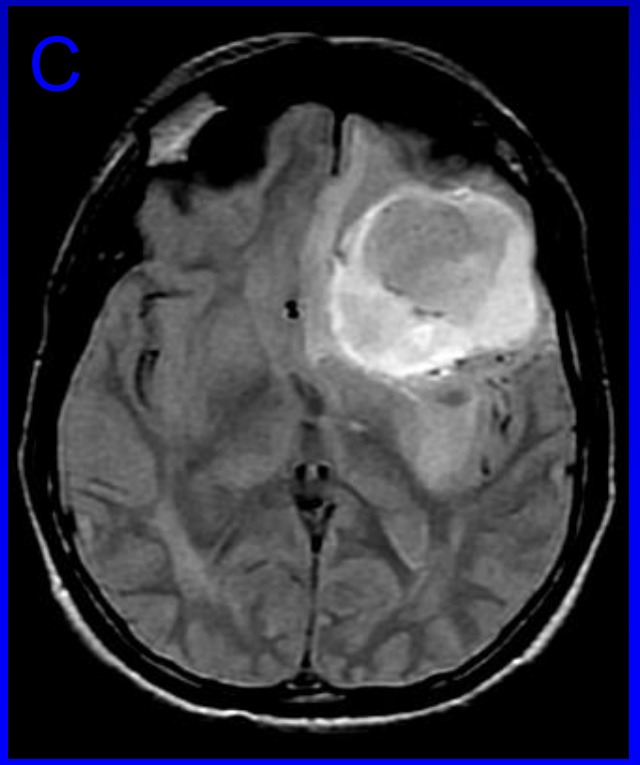
- Grade 1 / JPA
  - Occurs in children and highly curable
  - Treatment usually surgery alone
- Grade 2 / IDH mut + 1p19q codel – oligo
  - Adults in 40s
  - Incurable but median survival ~ 14 years
- Grade 3 / IDH mut + 1p19q non-codel – anaplastic astrocytoma
  - Adults in 50s
  - Incurable and median survival ~ 7 years
- Grade 4 / IDH WT – glioblastoma
  - Adults in 60s
  - Extremely aggressive with median survival ~ 18 months

Imaging features

- Oligo/Grade 2 → T2 bright, nonenhancing
- AA/Grade 3 → T2 bright, sometimes enhancing
- GBM/Grade 4 → T2 bright with significant edema, and heterogeneously enhancing

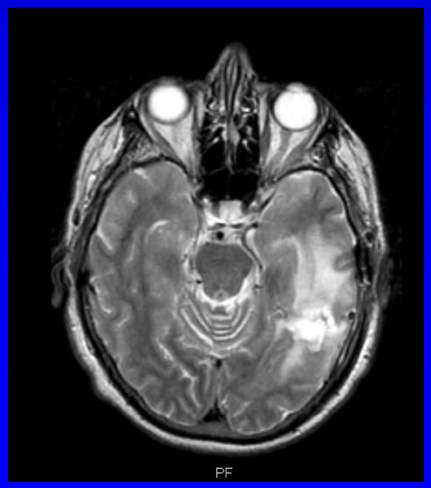

B

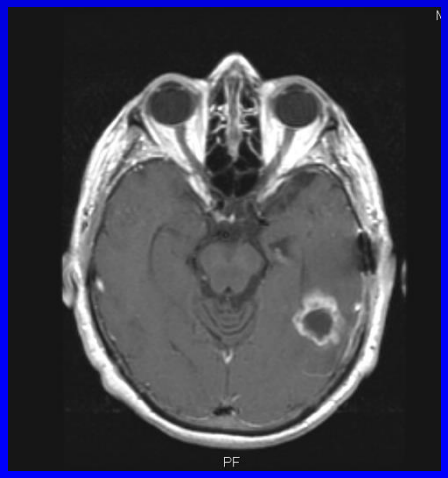

A


C

Radiology

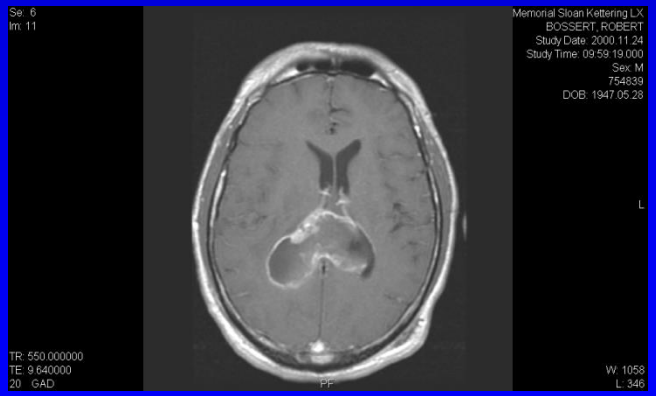
- GBM is typically heterogeneous, with central areas of necrosis surrounded by thick irregular walls of solid, living, neoplastic tissue. The gross tumor is surrounded by extensive, perilesional, vasogenic edema ("fingers of edema") and usually exerts considerable mass effect.

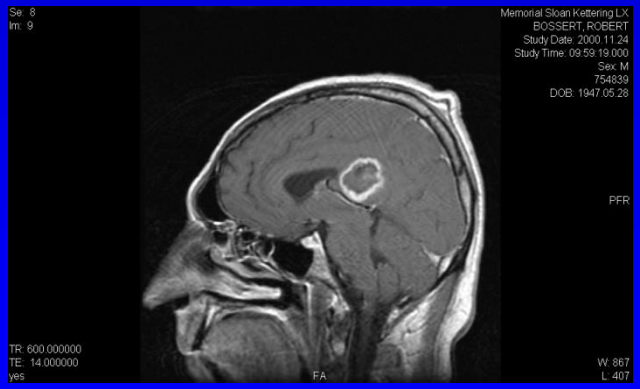


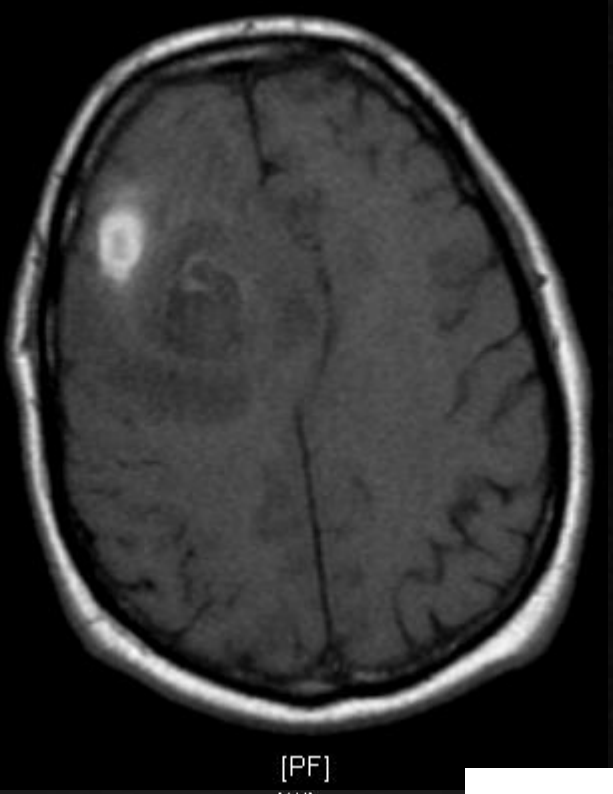


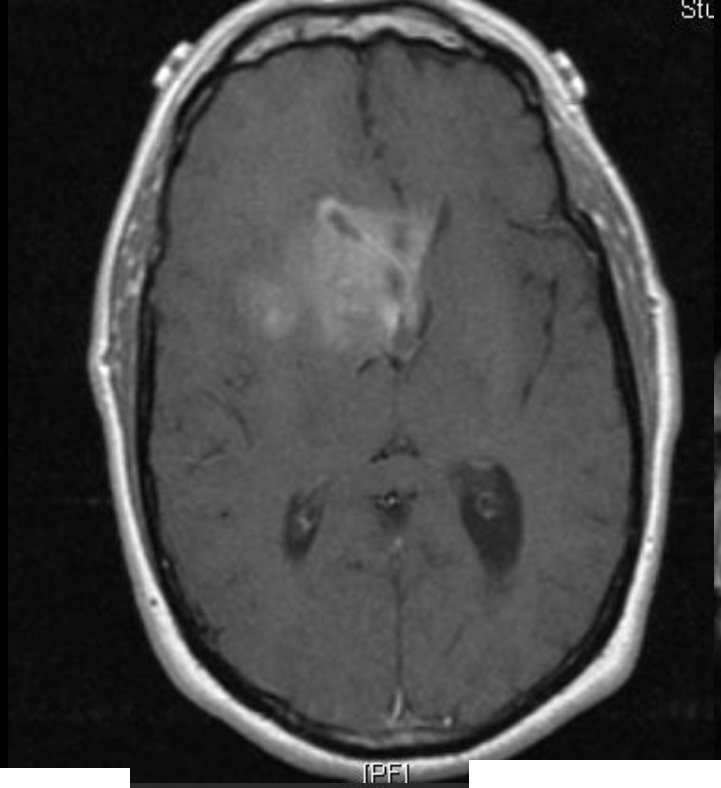
Radiology

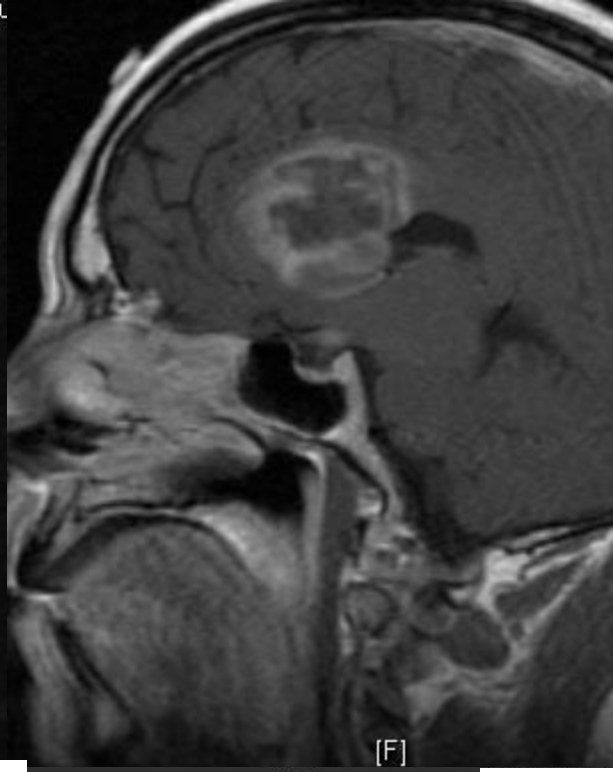
- enhanced T1-weighted image shows an irregular, thick-walled enhancing mass with central nonenhancing regions corresponding to necrosis.

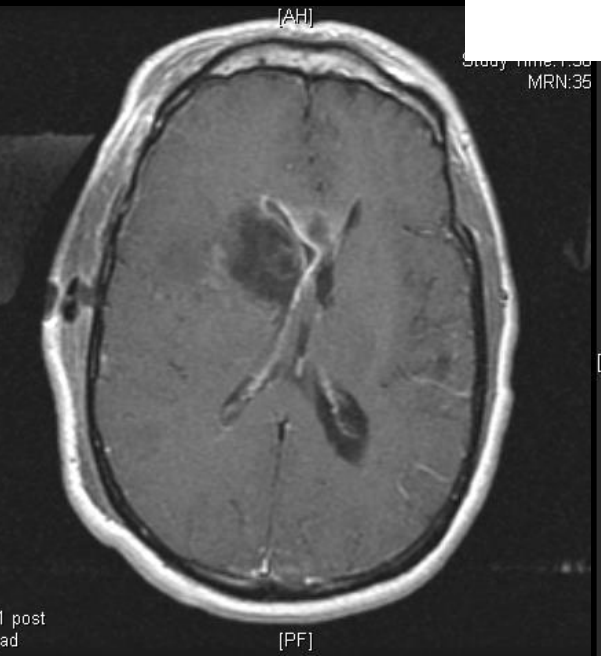


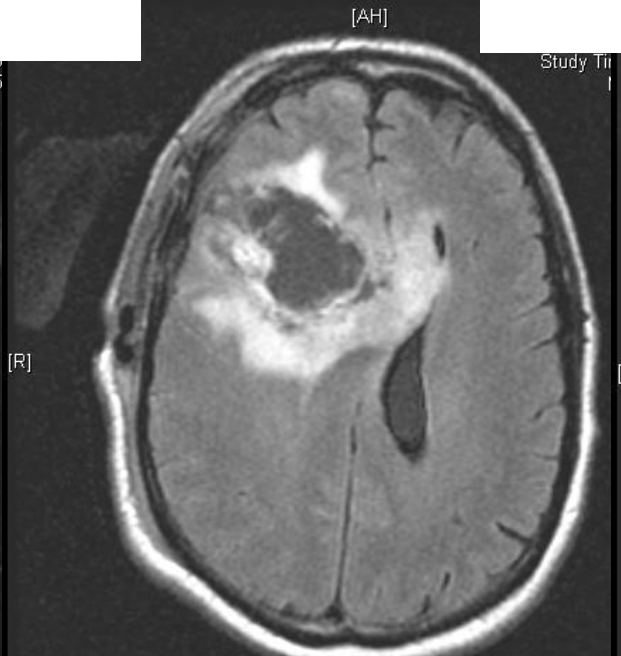


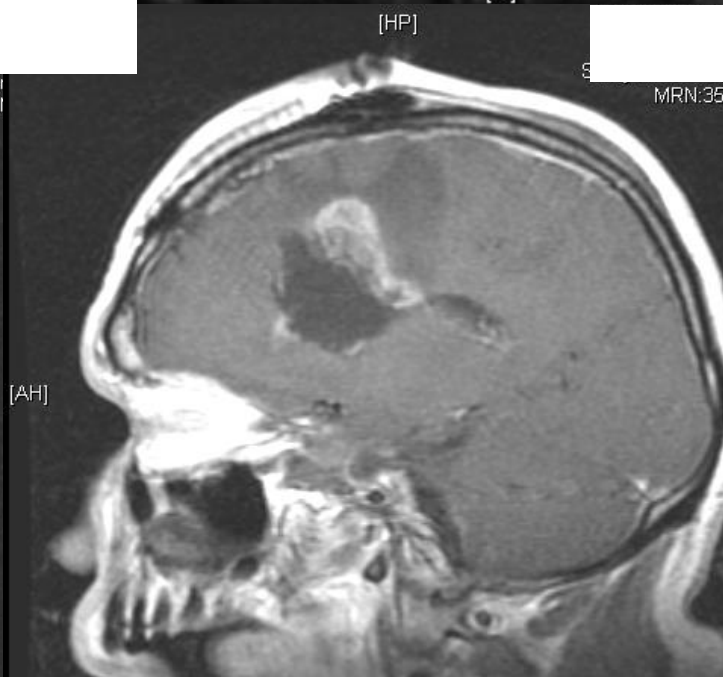

[PF]


[PF]


[F]


[AH]
MRN:35
[PF]


[AH]
[R]


[HP]
MRN:35
[AH]

Management of Glioma

- Grade 1 → surgery alone
- Grade 2 → surgery, RT, chemo (sequential)
- Grade 3 → surgery and chemoradiation
- Grade 4 → surgery and chemoradiation

Prognostic Factors

- Age at diagnosis <50 yrs vs. > 50 yrs
  - May be more important than histology
- Performance status
- Histology AA vs. GBM
- Treatment
  - Often influenced by above prognostic factors.

Surgical resection

- Surgery required for all patients
  - Biopsy at minimum to establish diagnosis
  - Maximal safe resection preferred sincee xtent of surgery is prognostic in some series
  - **RTOG (Simpson, IJROBP, 1993)**
    - Difference in median survival was also found for partial resection versus biopsy only treatment (10.4 vs. 6.6 months). There was no difference in survival for the different tumor sizes.
  - **MAYO (Devaux BC, J Neurosurgery, 1993)**
    - 196 newly diagnosed patients with cortical and subcortical tumors, grade IV glioma patients undergoing resection of the contrast-enhancing mass (CT or MRI) and postop XRT lived longer than those undergoing biopsy only and radiation therapy (median survival time 50.6 wks and 33.0 wks, $p = 0.03$).

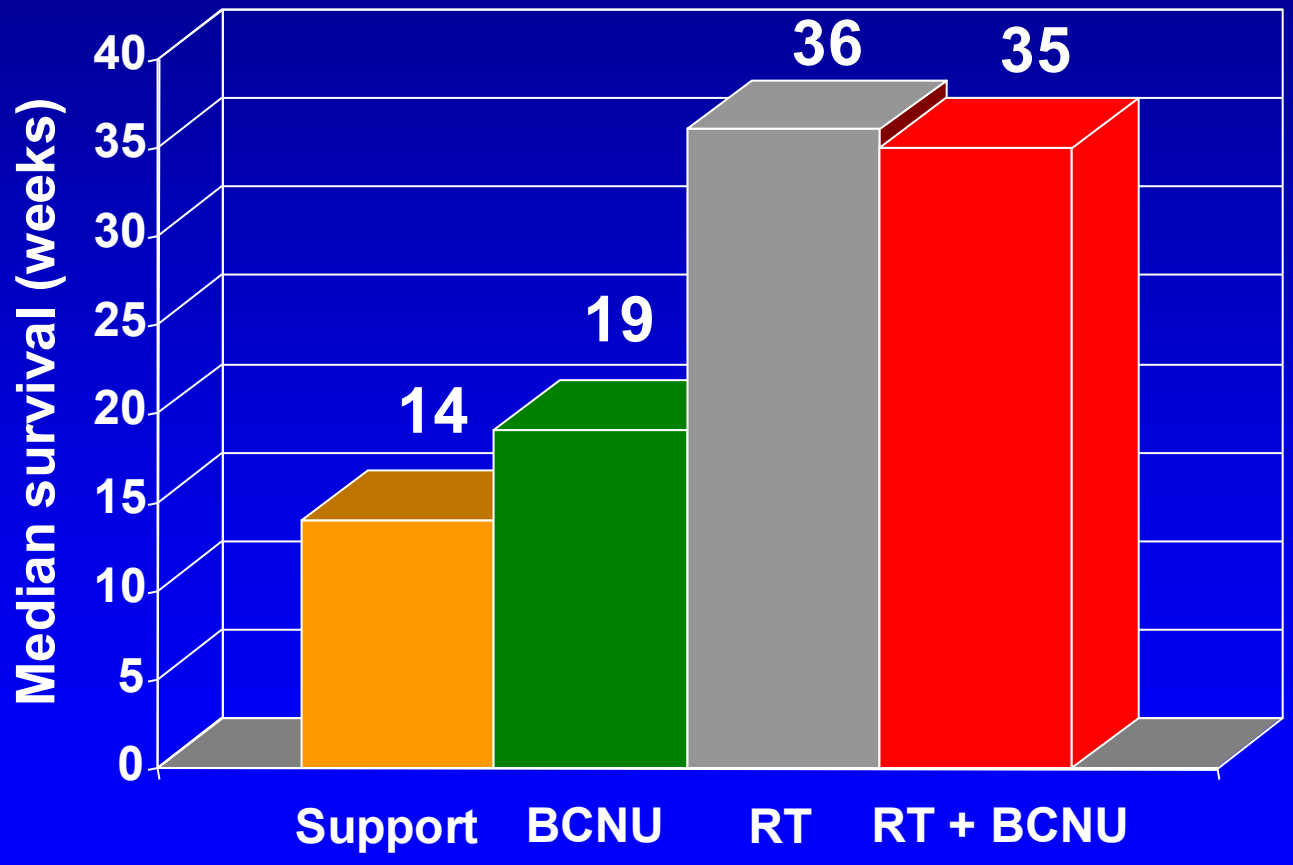
Surgery

- Secures diagnosis
- Alleviates ICP
- Reduces need for extended corticosteroids
- Median survival after surgery alone for GBM
  - 4 months.

Extent of Surgery

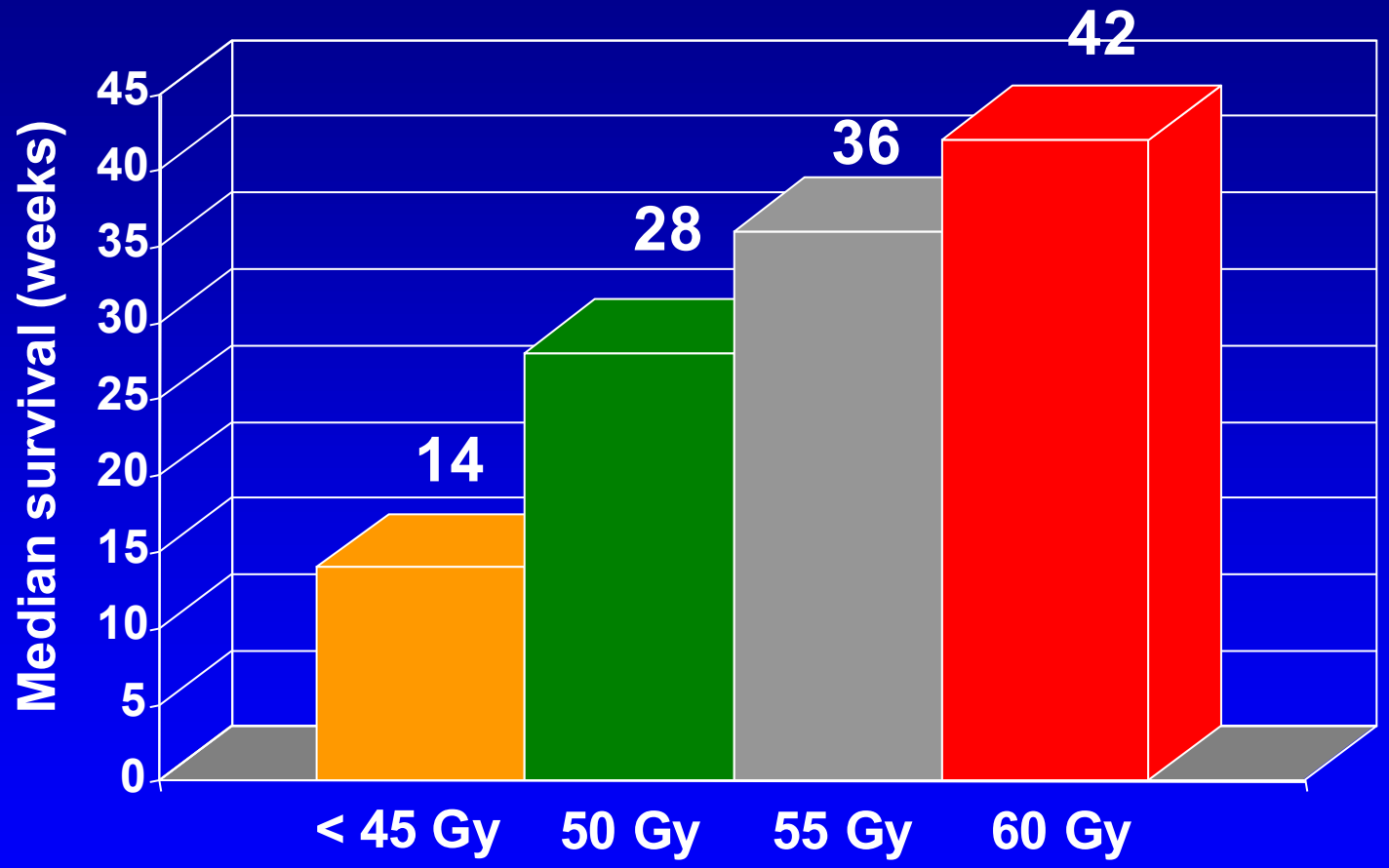
- Extent of surgery significant in retrospective series.
- RTOG recursive partitioning:
  - extent of surgery significant in only those over 50 years old and KPS = 70.
- Extent of surgery may impact on QOL
  - aggressive resection improved or delayed decline in KPS

Outcome of Randomized Trial (BTCG-6901) Testing the Efficacy of Radiation Therapy for Malignant Gliomas



Supportive care vs radiotherapy, $p = 0.001$

Relationship Between Radiation Dose and Survival in Malignant Gliomas



From: Walker, Strike and Sheline; 50 Gy vs 60 Gy, $p = 0.004$

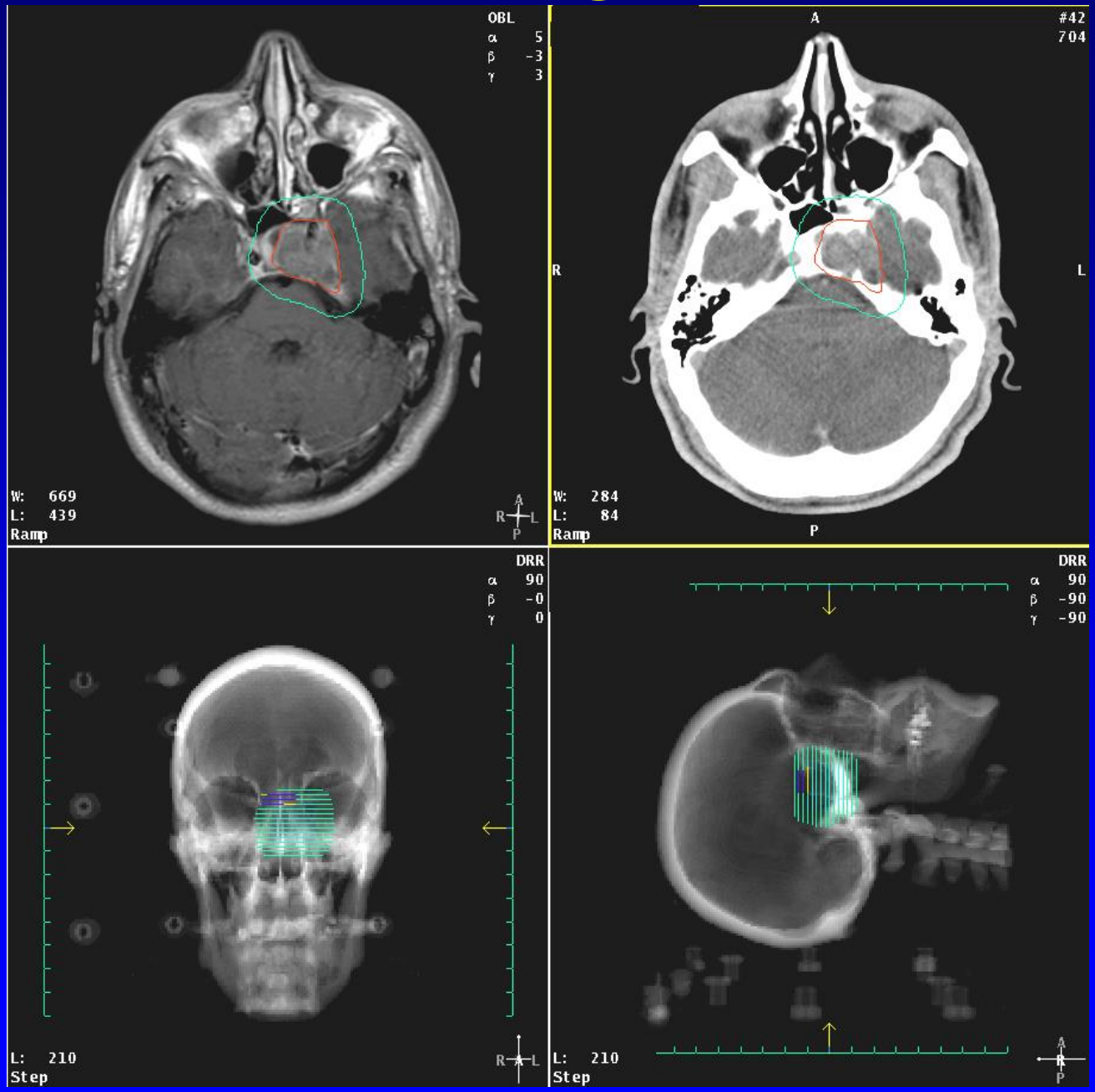
HGG: Adjuvant XRT

- No advantage with doses > 60Gy
  - Conventional 10 Gy boost, p=NS (RTOG 74-01)
- No advantage with SRS boost added to partial brain RT (RTOG 93-05, Souhami)
- No advantage with hyperfractionation (RTOG 90-06)
- Radiosensitization
  - (Hydroxyurea, misonidazole, etanidazole, IUDR,BUDR,DFMO) p=NS

Radiotherapy

- Grade 1 → only for recurrence, unresectable
- Grade 2 → usually done sequentially after surgery (54Gy)
- Grade 3 → immediate sequential or concurrent chemoradiation (59.4Gy)
- Grade 4 → concurrent chemoradiation with temozolomide (60Gy)

MR-CT Image Fusion



Chemotherapy for Malignant Gliomas

- Chemotherapy may not penetrate blood brain barrier well
  - use of surgically implanted wafers investigated
- Chemotherapy may be toxic to the normal brain
- No agent proven superior to BCNU until temozolamide

GBM: TEMODAR+RT improves OS

- EORTC/NCIC trial
  - 573 pts, GBM only, 2000-2002
  - Surgery → XRT (60 Gy/30 fxs/6wks)
    → XRT + Temodar

    Temodar:
    - 75 mg/m^2, 7 d/wk during RT,
    - f/b 6 cycles (150 to 200 mg/m^2 for 5 days each 28-day cycle).
  - Results:
  - Median survival: 14.6 mo (Tem) vs 12.1 mo
  - 2 yr-OS: 26.5 % (Tem) vs 10.4% ($p<0.001$)

Stupp, NEJM, 2005

Side Effects of Partial Brain RT

Acute:

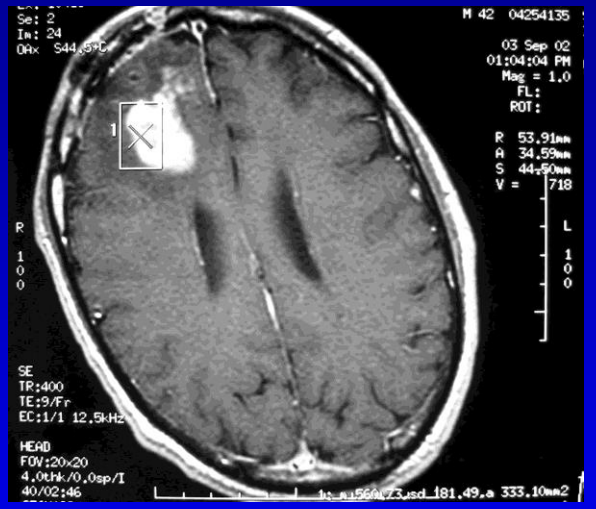
- Transient raised increased intracranial pressure
- Nausea, vomiting
- Steroid dependence
- Fatigue
- Skin reaction, alopecia

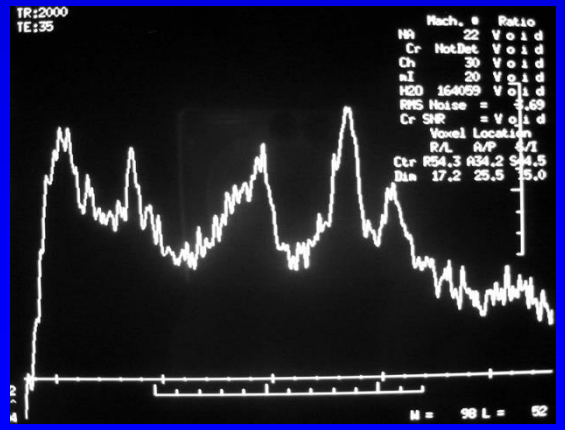
Late:

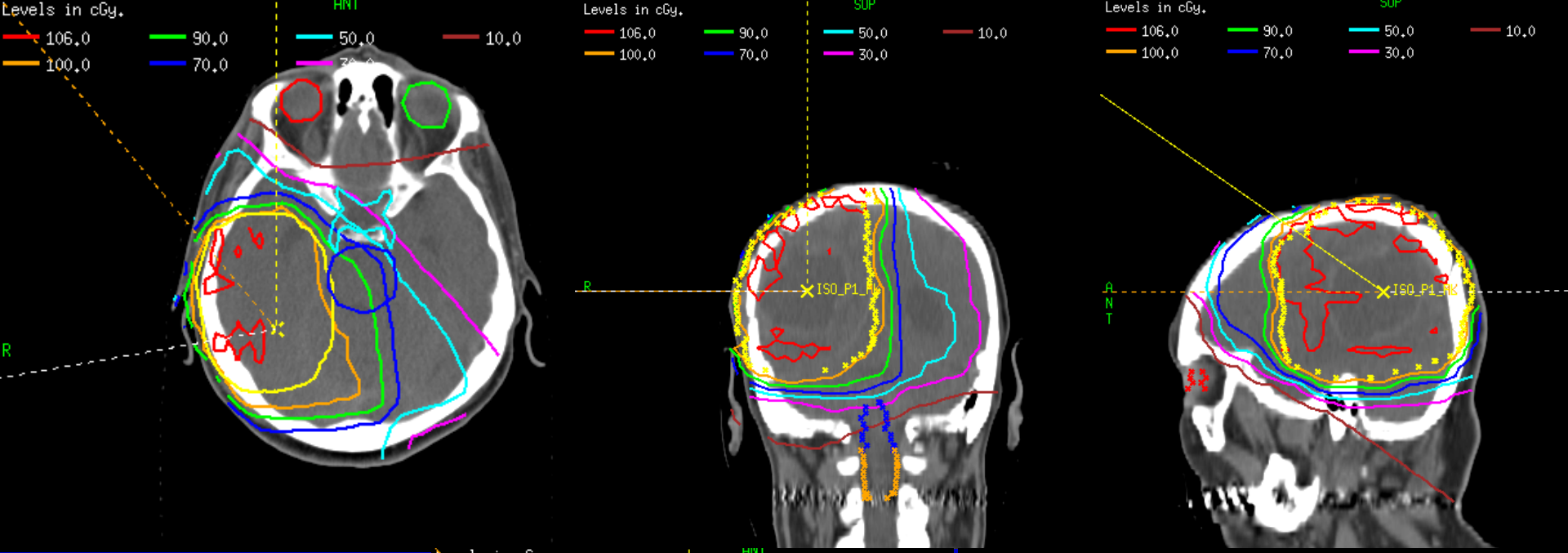
- Diffuse white matter injury
- Cerebral cortical atrophy
- Telangiectasia
- Decreased intellect
- Pituitary dysfunction
- Radiation necrosis

Radiation Necrosis

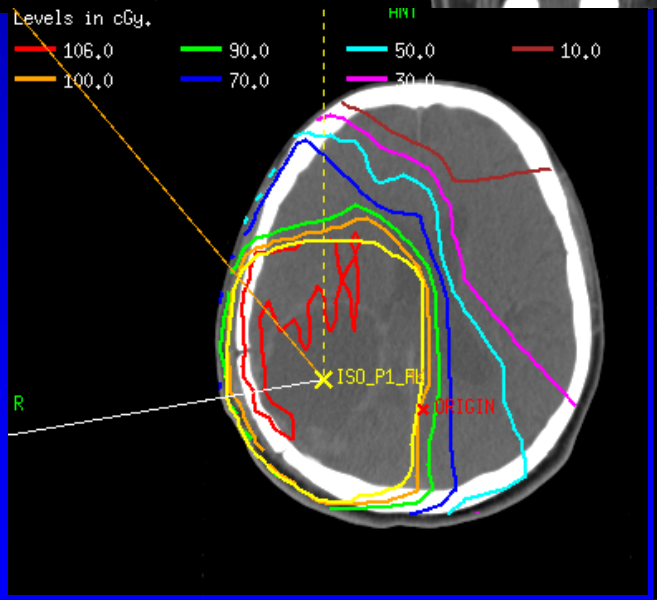
- Incidence – 3-9%
- Latency – 1-2 yrs post RT
- Imaging - MRI,PET,MRS
- Path – coagulation necrosis, demyelination
- Treatment – Decadron, surgery

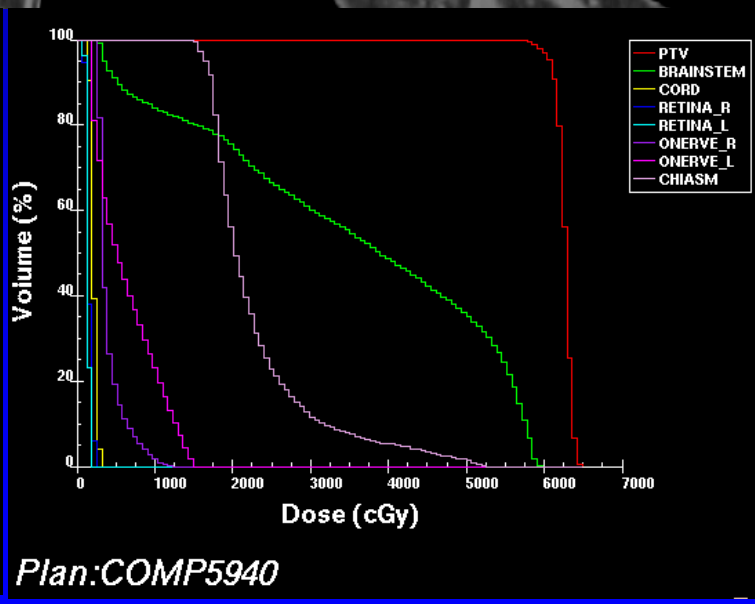






- Intensity modulated radiation therapy (IMRT) treatment plan for a patient with high grade glioma of right parietal region.





Meningioma

- Most common benign CNS tumor
- Incidence increases with age (peak 6th decade)
- F:M ratio is 2-3:1
- Cause
  - **99% idiopathic, 1% prior XRT, NF 2**

Pathology

- **Benign - 75-85% (WHO 1)**
- **Benign with atypical features 10-15%**
- **Atypical - 5-10% (WHO 2)**
- **Anaplastic (malignant) - <5% (WHO 3)**

Slide courtesy of JSL

Meningioma

- Location
  - Central – 50% failure following surgery only
  - Convexity – 10% failure following surgery only
- Good prognostic factors
  - Benign histology (Grade 1)
  - Complete resection
  - PR or PR/ER receptor positive
- Less favorable prognostic factors
  - Histology other than benign
  - Less than complete resection
  - No PR or ER receptor or ER alone
  - MIB-1 >3-4%
  - Bone invasion

Slide courtesy of JSL

Imaging Characteristics

- extra-axial, smooth, well-circumscribed, homogeneously-enhancing
- bone destruction or hyperostotic changes
- dural tail (~50-60%)
- 20% with calcifications

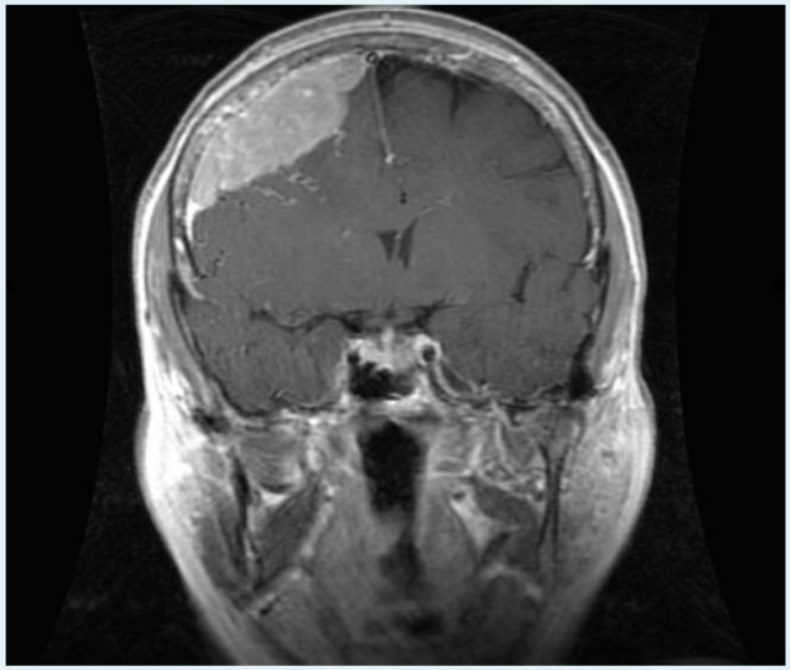
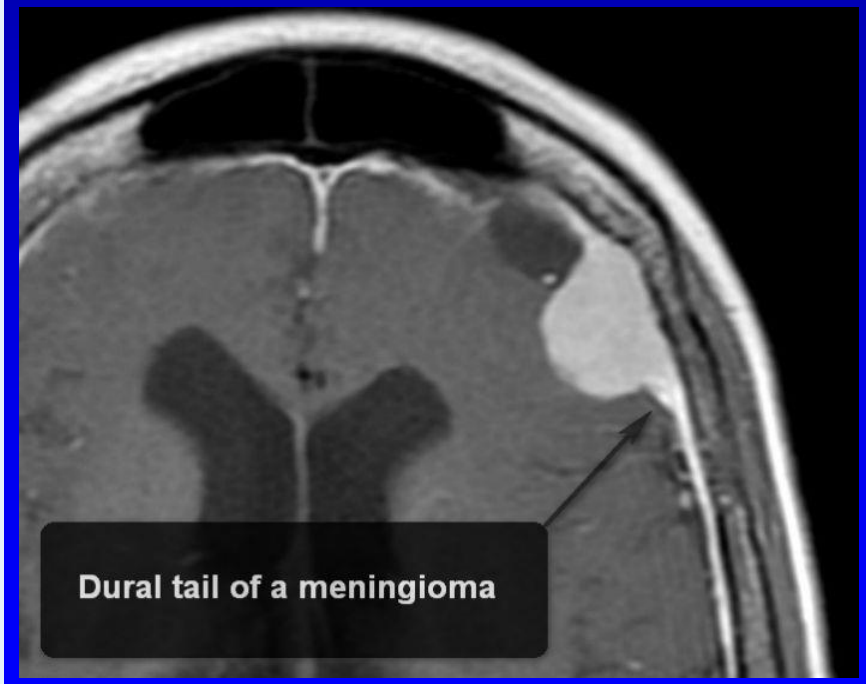
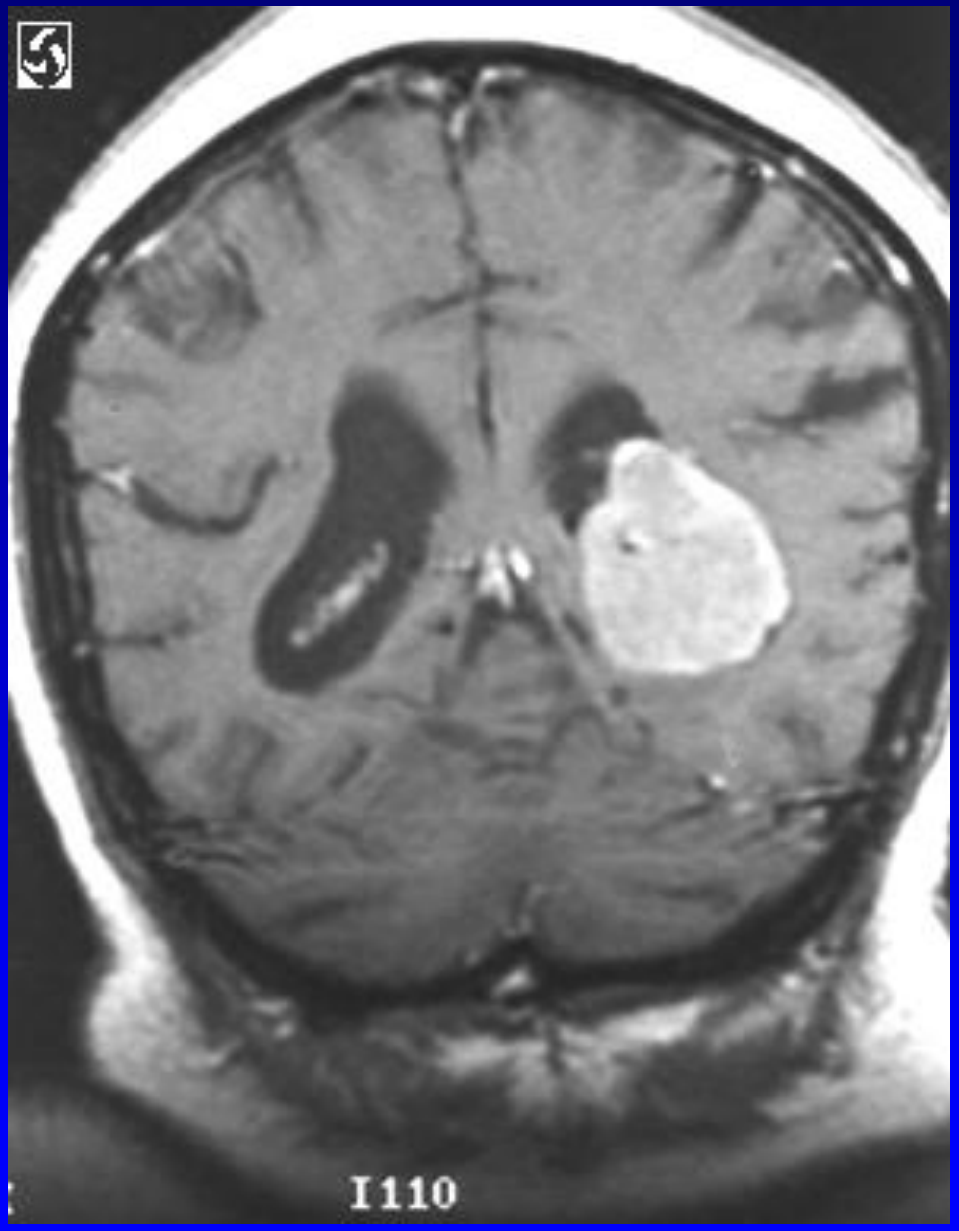


FIGURE 4: T1-weighted MRI with gadolinium contrast showing the typical appearance of a meningioma. Note the dural-based 'tail.'



Meningioma

- Most frequent locations along the sagittal sinus and over the cerebral convexity.
- They often also produce hyperostosis; bony invasion does not indicate malignancy.



NF2 bilat acoustic neuromas, neurofibromatosis, mening.

(NF1 optic glioma, café au lait)

EBRT- 54 Gy low grade

(59.4 Gy high grade)

CTV=GTV & hyperostotic bone

1 cm margin low gr

2-3 cm margin high gr

If smaller,

SRS 12-13 Gy low gr (don't do SRS for high grade, can SRS boost)

LC >90%, 50% high gr

Management Summary

Small, asymptomatic tumors → observation

Large, symptomatic tumors → treatment

maximal safe resection

Grade I GTR → observation

Grade I STR → observation vs RT

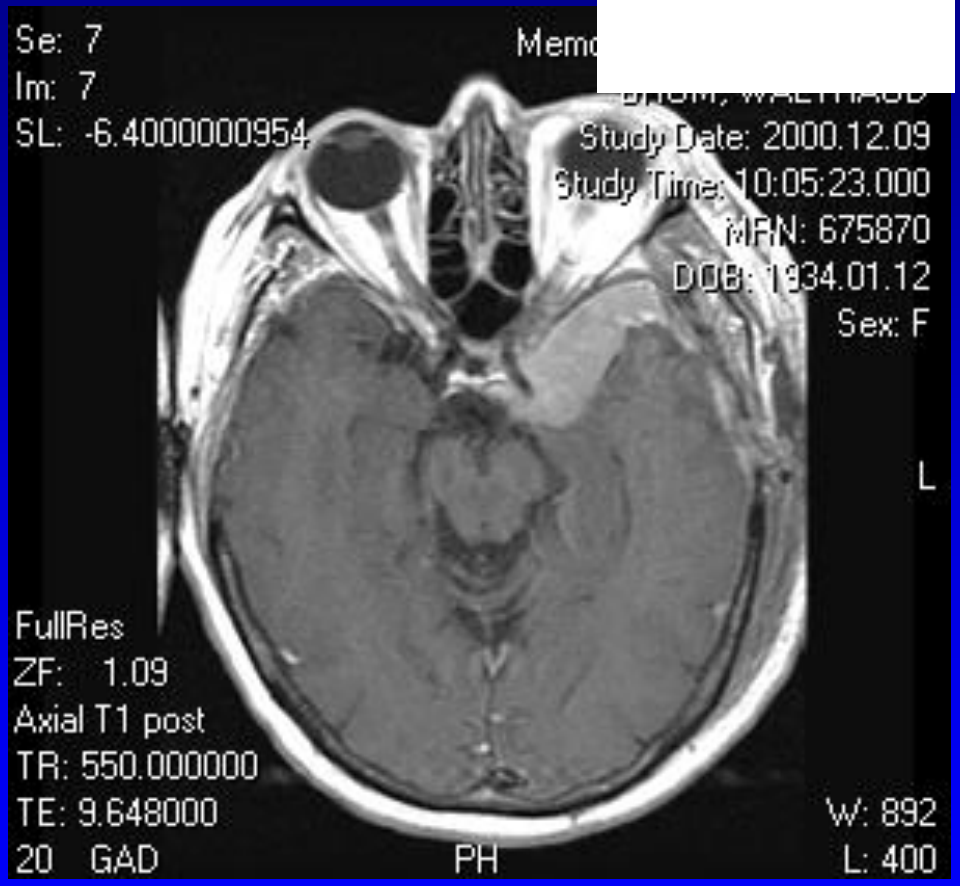
Grade II/III → adjuvant RT

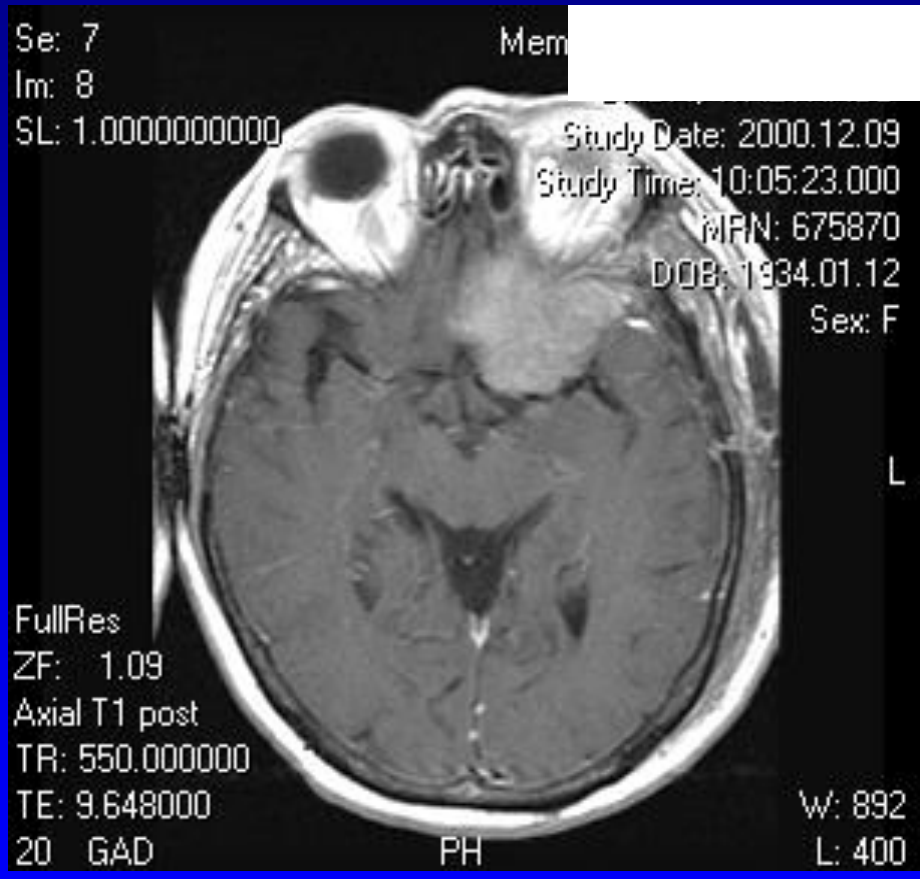
recurrence → surgery vs RT

definitive radiation

fractionated RT vs SRS

Meningioma


Se: 7
Im: 7
SL: -6.4000000954
Study Date: 2000.12.09
Study Time: 10:05:23.000
MRN: 675870
DOB: 1934.01.12
Sex: F
L
FullRes
ZF: 1.09
Axial T1 post
TR: 550.000000
TE: 9.648000
20 GAD
PH
W: 892
L: 400


Se: 7
Im: 8
SL: 1.0000000000
Study Date: 2000.12.09
Study Time: 10:05:23.000
MRN: 675870
DOB: 1934.01.12
Sex: F
L
FullRes
ZF: 1.09
Axial T1 post
TR: 550.000000
TE: 9.648000
20 GAD
PH
W: 892
L: 400

Surgery

- Goal of meningioma surgery is total resection, because this is often curative for benign tumors
- ***total resection*** is followed by 7% recurrence rate at 5 years, 20% at 10 years, and 32% at 15 years

Pituitary Adenomas

- Present in 25% of people at autopsy (incidental)
- Classified on size and function
  - Microadenoma (<1 cm). Cure with surgery > 80%
  - Macroadenoma (>1 cm). Cure with surgery < 50%
  - Silent or non-functioning (large lesions - mass effect –visual field deficits)
  - Hormonally active (small lesions – biochemical manifestations)
- Predictors of recurrence following surgery
  - Radiographic evidence of invasion
  - IGF-1 level in Acromegaly and urine free-cortisol in Cushing's
  - P53 status
  - Labeling index

Slide courtesy of JSL

Presentation

- Tumors smaller than 10 mm (microadenomas) rarely compress the optic apparatus.
- Larger tumors >1cm are called macroadenomas. Further growth can involve the cavernous sinus bilaterally, the third ventricle (sometimes producing hydrocephalus), and sometimes the middle, anterior, or even posterior fossae.
- Classic ophthalmologic finding is visual loss, typically starting with bitemporal hemianopsia and loss of color discrimination.
- Extraocular palsies can result from compression or invasion of the nerves of the cavernous sinus. (deviation of eye laterally 6^{th} nerve)

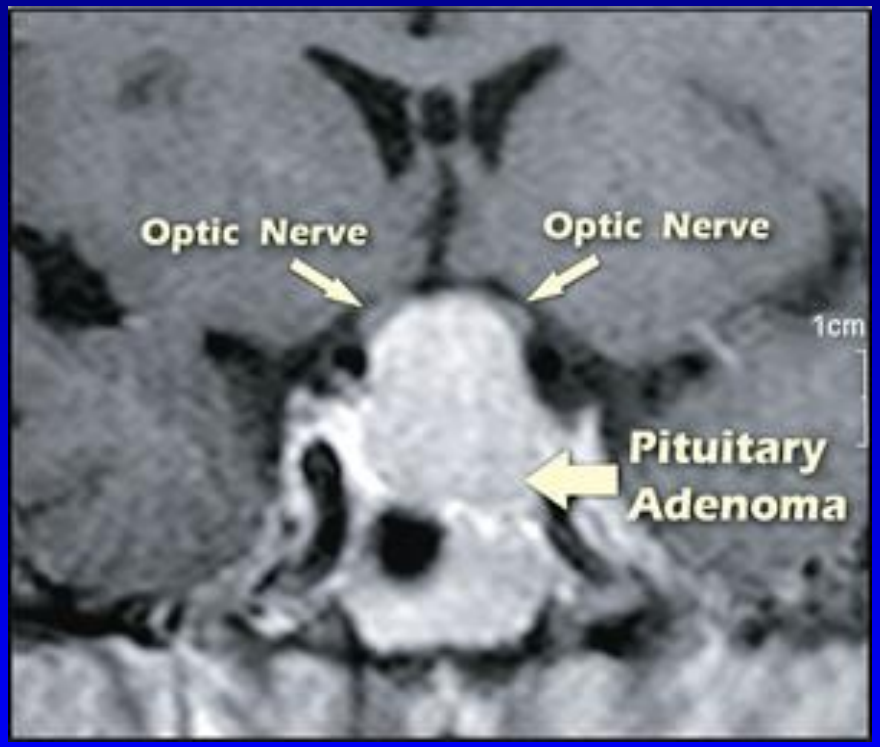
Presentation

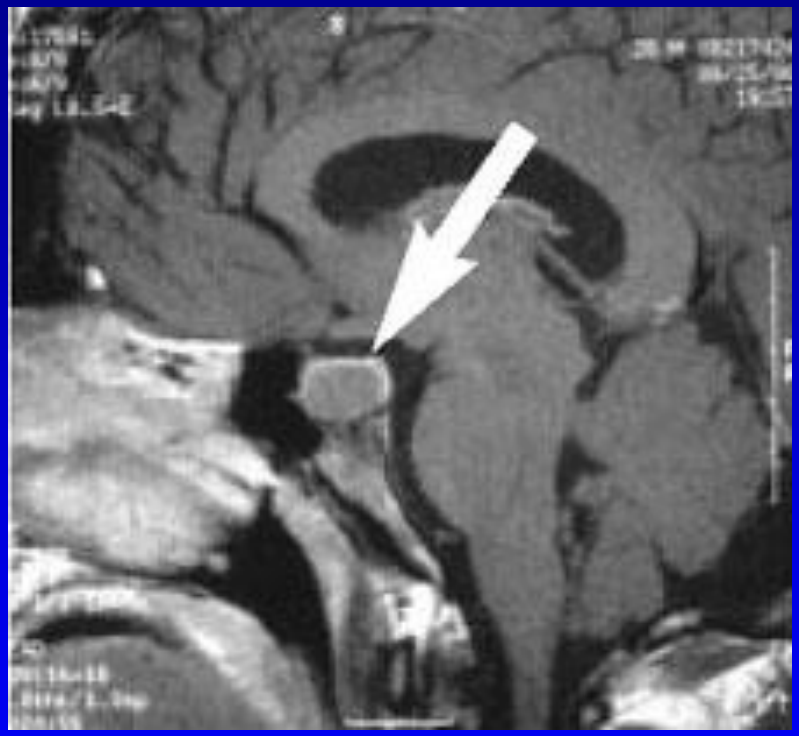
- Neuroendocrine abnormalities usually indicate an endocrinologically active tumor that oversecretes pituitary hormones but can also result from tumor compression of the pituitary gland.
- The most common endocrinologically active tumors secrete prolactin, adrenocorticotropic hormone (ACTH), or growth hormone.
- Sexual impotence in men and amenorrhea and galactorrhea in women are hallmarks of a prolactin-secreting tumor.
- Hypogonadism, infertility, and osteopenia are also common.
- Growth hormone hypersecretion causes acromegaly (increased hand and foot size, macroglossia, frontal bossing, etc.). Soft tissue swelling, peripheral nerve entrapment syndromes, and arthropathies occur.
- Elements of hypothyroidism, adrenal insufficiency, and growth hormone deficiency may follow compression of the pituitary gland by an adenoma.

Medical Treatment for Pituitary Adenomas

- Dopamine agonists (e.g., bromocriptine or cabergoline) are the most effective therapy for prolactinomas and are used as primary treatment
- Somatostatin analogue (either short acting or long acting) is effective medical therapy for patients with acromegaly

Pituitary Adenoma





Pituitary Adenoma

- Management
  - Surgery
  - Radiation Therapy
  - Chemotherapy
  - Endocrinologic
- 90% local control with radiotherapy

Side Effects of RT

- Common to have Hypopituitarism post RT
- Hypopituitarism is largely correctable by hormone replacement therapy, and patients treated for pituitary adenomas should have lifelong endocrine follow-up
- The risk of developing a radiation-induced brain tumor after treatment is 1.3% to 2.7% at 10 years and 2.7% at 30 years

Appendix

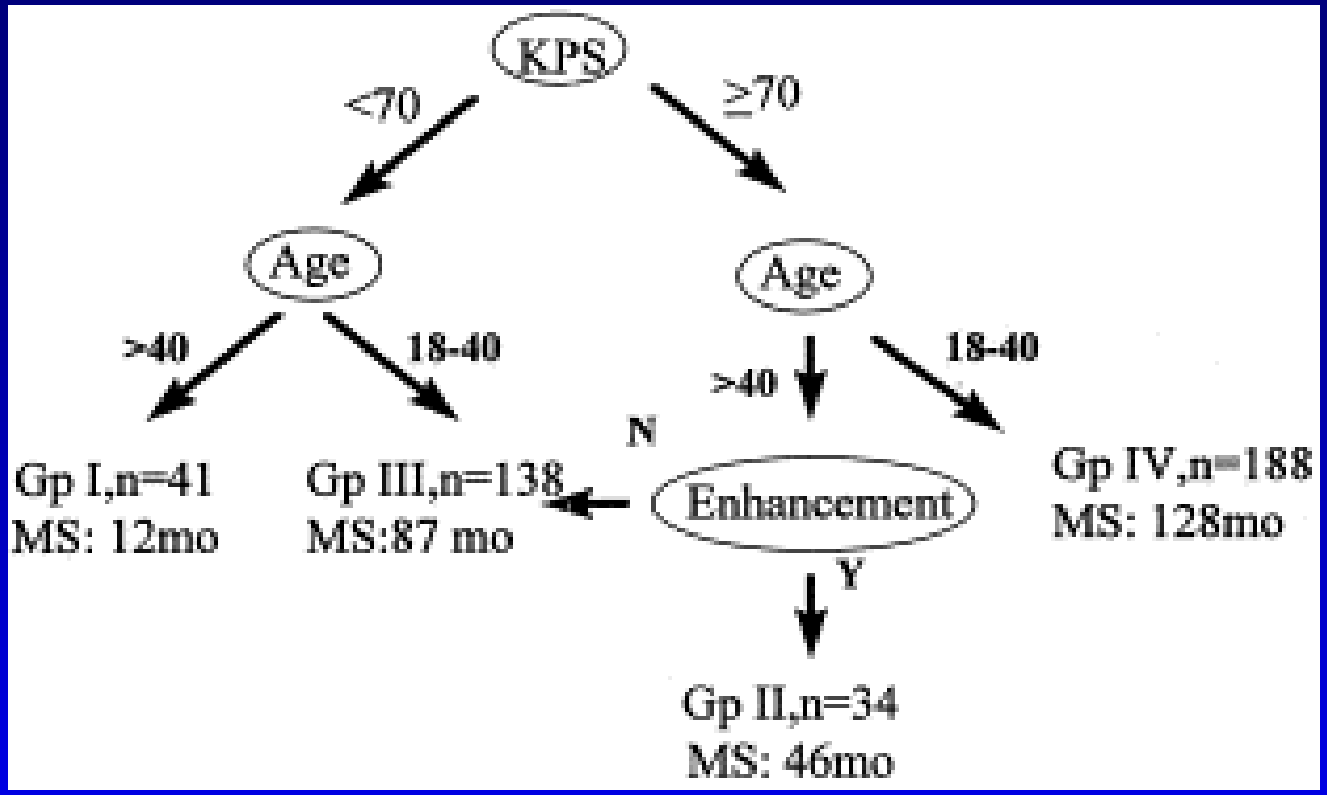
Low Grade Glioma
Diffuse Astrocytomas (WHO II)

- Peak incidence 20-50 yrs
- Occur primarily in cerebral hemispheres
- Age is most powerful predictor of OS
  - Age at diagnosis of low-grade astrocytoma is inversely correlated with time to progression
  - Ageing-related impairment of DNA repair and the resulting acquisition of mutations may promote rapid progression after transformation occurs.
- Incidence of progression within astrocytomas is variable but can be as high as 80%.
- Median survival 7 yrs.

Low Grade Glioma: Pathology

- Infiltrative, with microscopic invasion of normal brain distant from the tumor epicenter.
- **Absent microvascular endothelial proliferation** and **necrosis.**
- Proliferative index, (MIB-1 Ab to Ki-67 Ag expressed only in proliferative stages of the cell cycle, is generally low, typically 2–4%.
- **Astrocytic** (3 variants: fibrillary, protoplasmic, gemistocytic astrocytomas)
- **Gemistocytic astrocytomas:** cells with abundant eosinophilic cytoplasm, amount seen in LGG is prognostic.
  - Low grade astrocytomas with >5% gemistocytes had shorter time to progression

LGG: Recursive Partitioning Analysis



401 ptns >18 yo, from LRCC, UCSF, NRH

Group	Patient Characteristics	Median survival (mo)
I	KPS <70, Age >40 y	12
II	KPS ≥70, Age >40 y, w/ tumor enhancement	46
III	KPS <70, Age ≤40 y, or KPS ≥70, Age >40 y, no tumor enhancement	87
IV	KPS ≥70, Age ≤40 y	128

(Bauman G, IJROBP, 1999)

LGG: Treatment

- **Surgery: histologic verification mandatory**
  - Gross total resection when possible
    - Advantage for GTR: complete histopath analysis, potentially curative, relief Sx.
    - Disadvantage for GTR: potential morbidity and indolent growth of tumor
  - Sampling error possible resulting in missing high-grade component
  - OS advantage has been demonstrated with GTR
    (Keles, J Neurosurg 2001;Claus, Cancer, 2005)

- **Adjuvant chemotherapy: No standard role**

- **Adjuvant RT: Controversial**
  - Argument for delayed XRT (for recurrence only)
    - RT causes side effects, short term QOL, neurocognitive, and hormonal dysfunction
    - Possible induction of malignant transformation
    - Loss of salvage therapy for progression
  - Argument for immediate XRT (post-op)
    - Immediate XRT improves PFS (EORTC 22845)
    - High XRT doses do cause neurologic sequelae and are not better than moderate doses (NCCTG, EORTC 22844)
    - Immediate XRT decreases seizure incidence