Target Delineation in Gliomas

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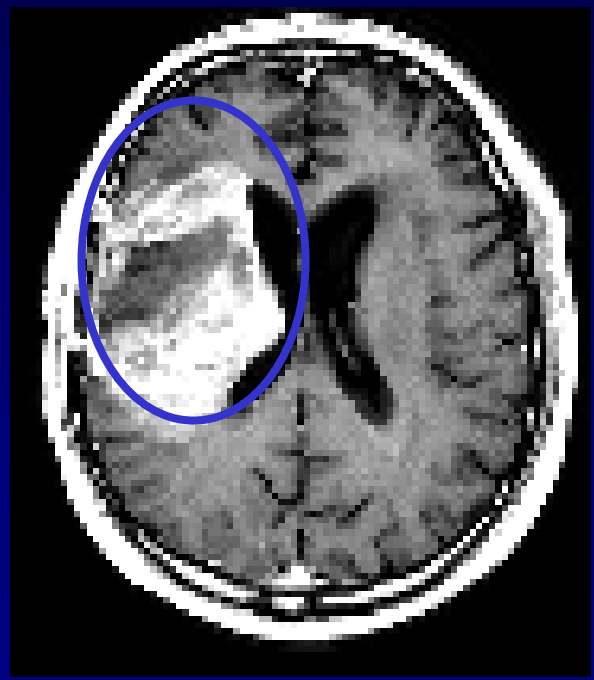
What is a *glioma*?

- A primary brain tumour that originated from a cell of the nervous system



Recommendations: Lowgrade Gliomas

Level I Grade A recommendation

- It is recommended that radiation therapy planning include a 1 cm margin around the radiographically defined FLAIR tumor volume(preferred imaging sequence).

- Doses preferred are from 50-54 Gy @ 1.8-2.0 Gy/#

Recommendations: Lowgrade Gliomas

Level III recommendations

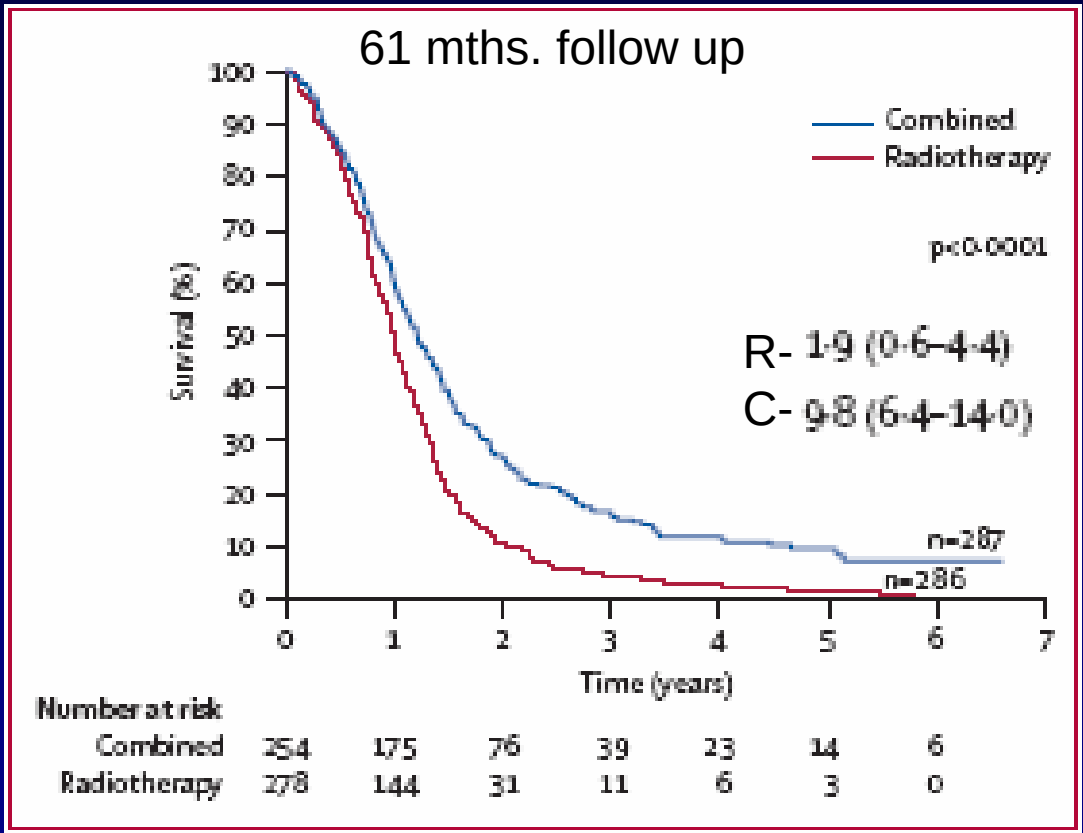
For LGGs of Optico –Hypothalamic Axis(OHA) and other eloquent areas stereotactic radiotherapy protocols should be implemented in order to decrease the late neuropsychiatric sequelae.

Recommendations: High grade Gliomas

Level 1, Grade A Evidence

- Radiation therapy along with temozolamide is recommended for the treatment of newly diagnosed malignant glioma in adults.
- Treatment schemes should include dosage of up to 60 Gy given in 2 Gy daily fractions that includes the enhancing area.

Combined modality in GBM



Stupp R et al. Lancet, March 9, 2009

Recommendations: High grade Gliomas

Hypo-fractionated RT – Pts. with a poor prognosis

- Limited survival without compromising response.
- Quality of life issues.

NOT RECOMMENDED

- Hyperfractionation & Accelerated fractionation
  - Not superior to conventional fractionation.
- Brachytherapy & SRT boost
  - No Advantage , not recommended .

Recommendations: High grade Gliomas

Level 2

- It is recommended that radiation therapy planning include a 1–2 cm margin around the radiographically defined T1 contrast-enhancing tumor volume

- T2 weighted abnormality on MR imaging.

Low Grade Glioma

- Heterogeneous disease group – WHO II
- Non Enhancing lesion on CT – MRI
  - Earlier diagnosis
- Incurable – long natural history
  - *Controversy - role –surgery – radiotherapy*
  - Chemotherapy
- Molecular biology – targeted Therapy

Prognostic factors in LGG

Prognostic Factor (reference level)
Age at randomization
< 40 years
≥ 40 years
Largest diameter of the tumor
< 6 cm
≥ 6 cm
Tumor crossing midline
No
Yes
Histology type
Oligo/mixed
Astrocytoma
Neurologic deficit
Absent
Present

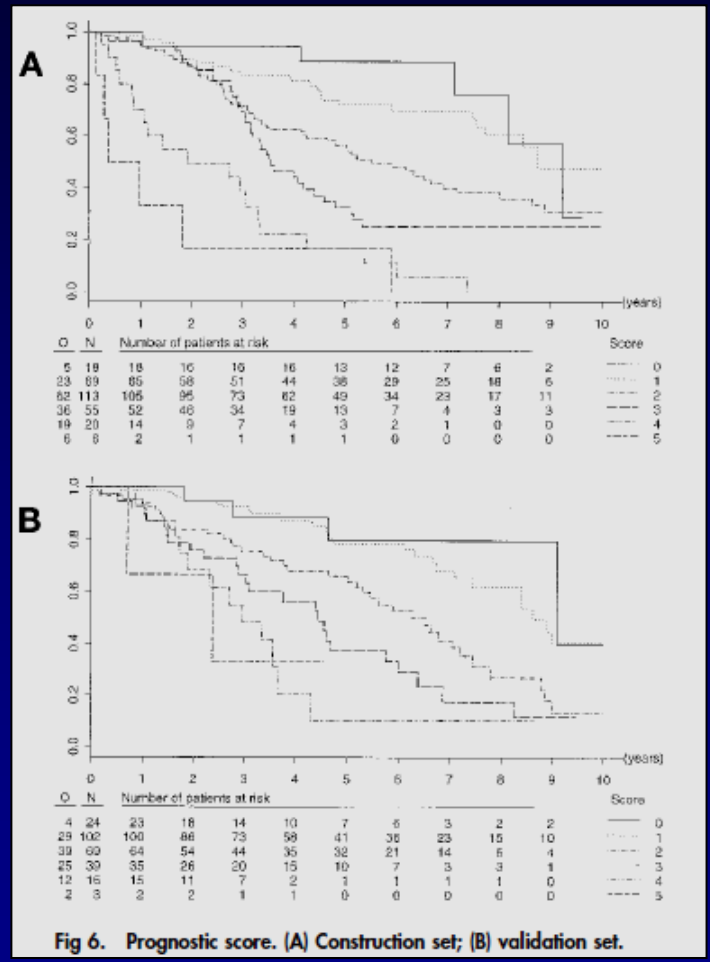
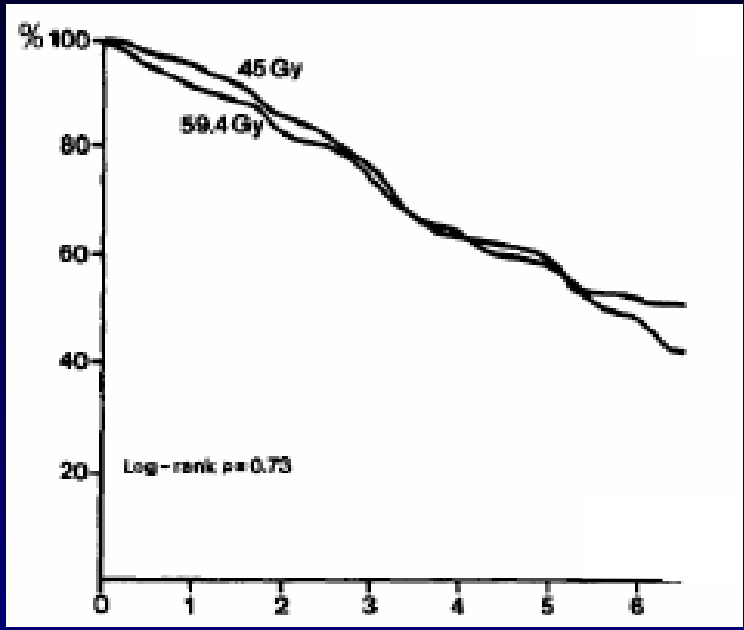


Fig 6. Prognostic score. (A) Construction set; (B) validation set.

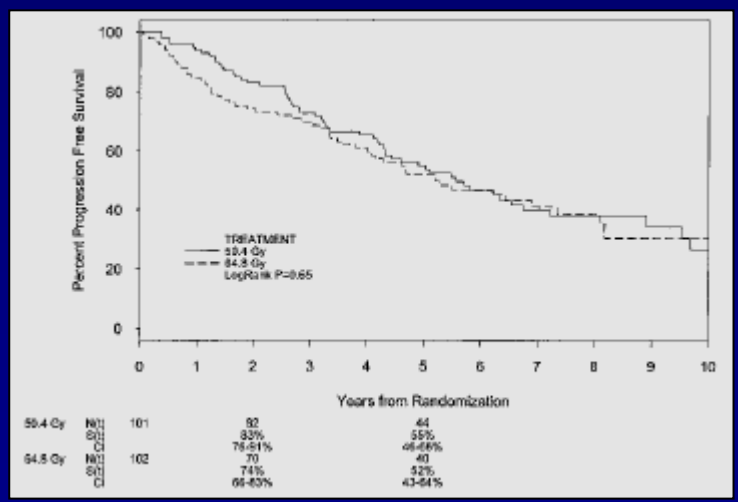
Pignatti, F. et al. J Clin Oncol; 20:2076-2084 2002

Radiotherapy: total dose



OS and PFS: no difference between lower (45-50 Gy) vs higher dose (59-65 Gy)

EORTC 22844
IJROBP 36:549-556, 1996



Accepted actual standard: 50.4 – 54 Gy

NCCTG/RTOG/ECOG J Clin Oncol 20:2267-2276, 2002

Current Problems with Anatomic Imaging

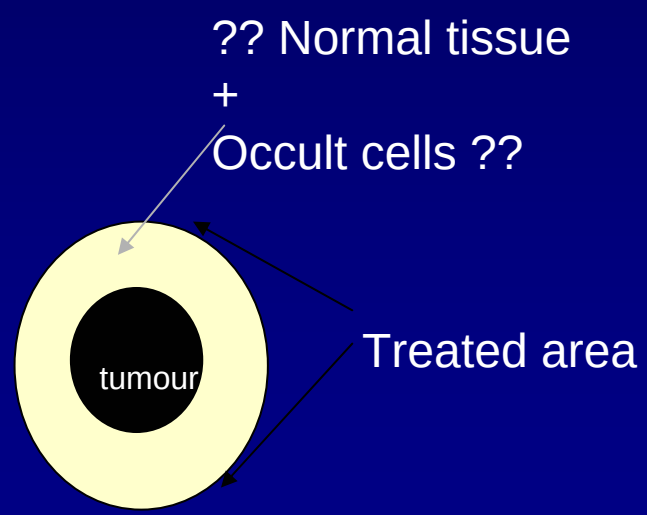
- Highly sensitive but nonspecific
- Cannot reliably differentiate tumor and treatment effects
- Unable to guide specific targeted therapy
- Cannot assess early therapy failure & predict clinical outcome
- Contrast enhancement is nonspecific
- GBM Abscess TB
- Demyelinating

Introduction

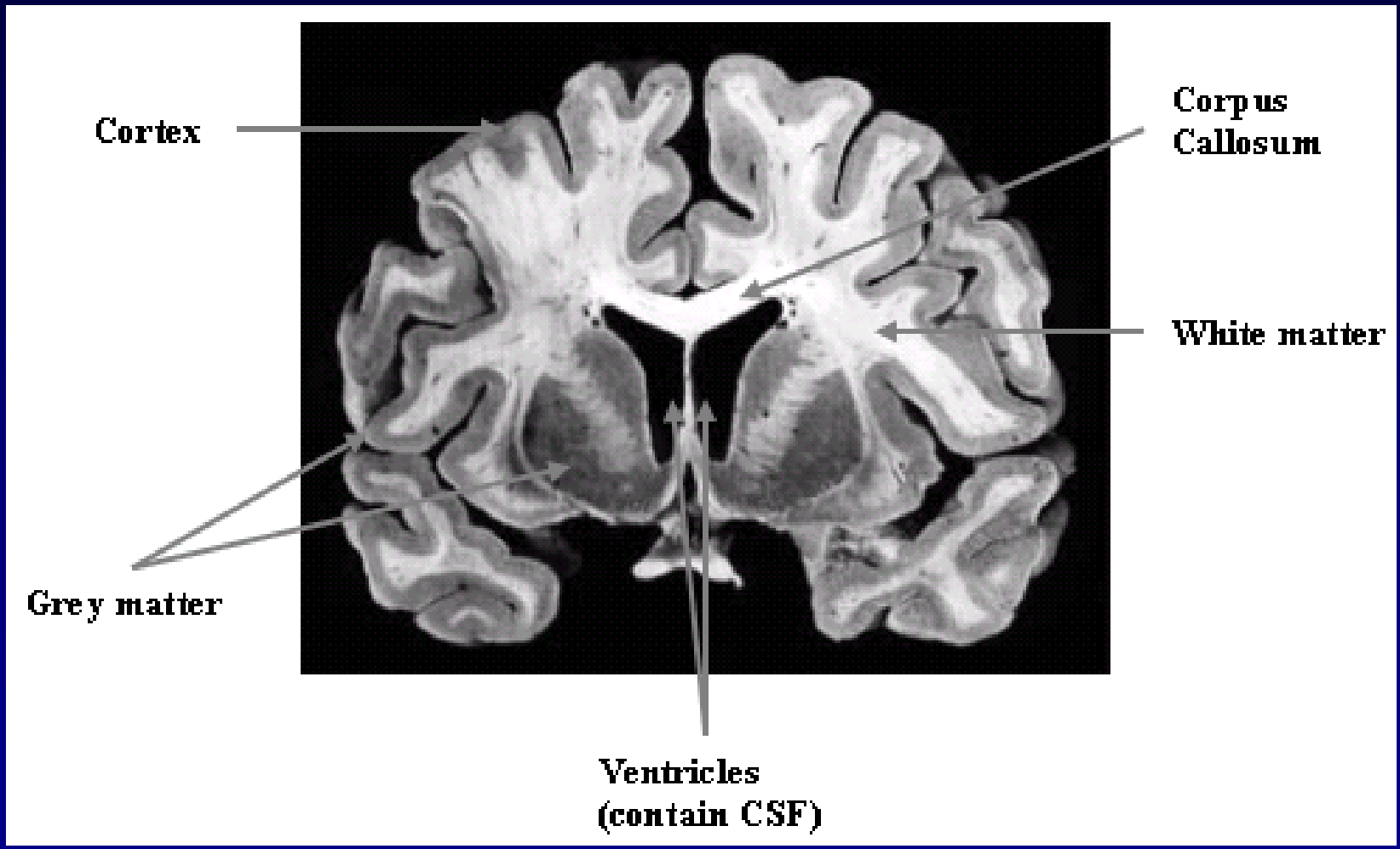
- Task: Where to irradiate!
- Brain Biology
- MRI
- Radiotherapy

Task

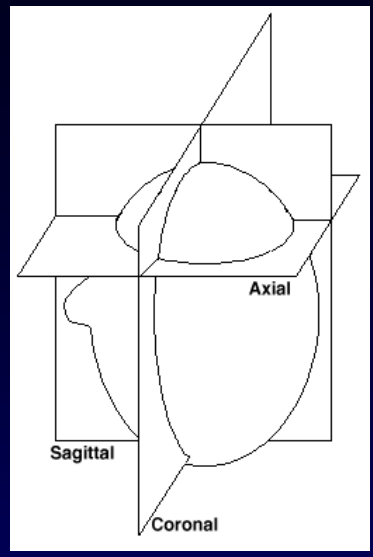
- Goal: *Effective radiotherapy of Brain Tumours*
  - *determine what region of brain to treat (irradiate)*
- Problem:
  - Just targeting visible *tumour cells* is NOT enough…
  - Must also kill "(radiologically) occult" cancer cells surrounding tumour !
- Current Approach:
  - Irradiate 3cm margin around tumour
  - Not known if
    - this area contains occult cells
    - ONLY this area contains occult cells

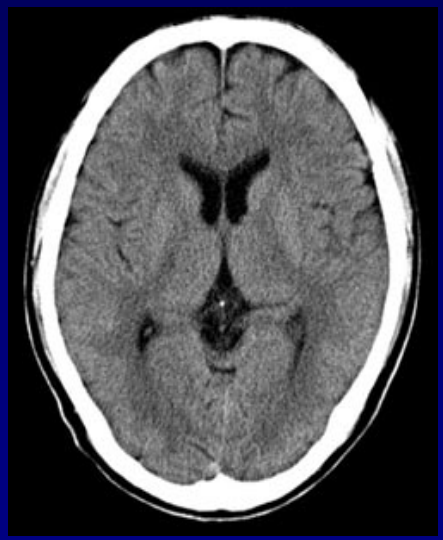


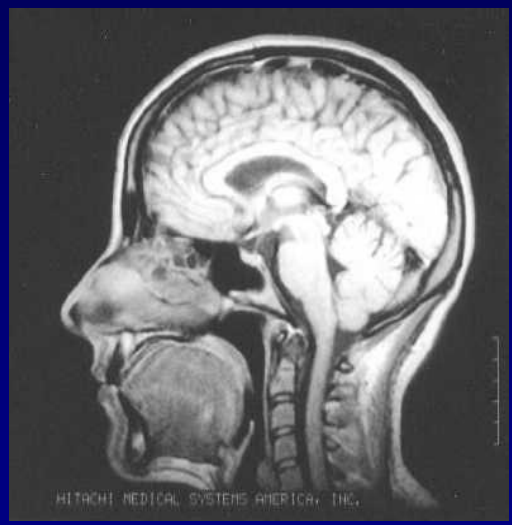
Brain Biology

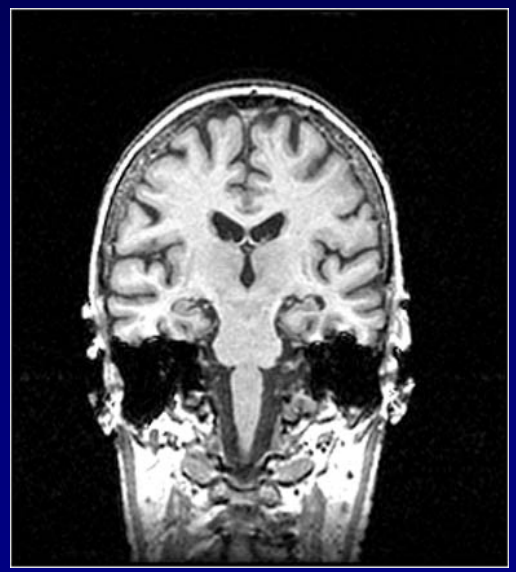


MRI – image views



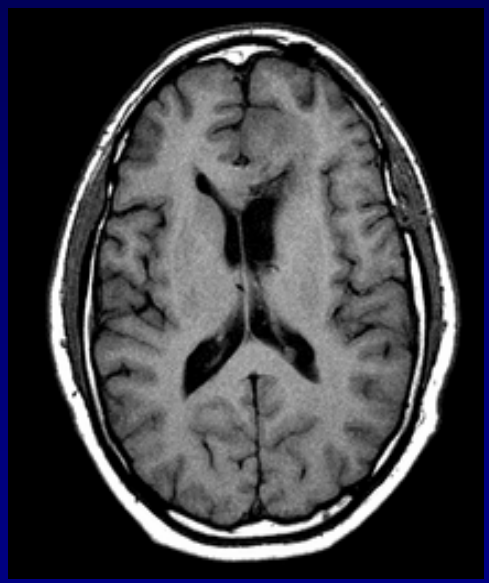




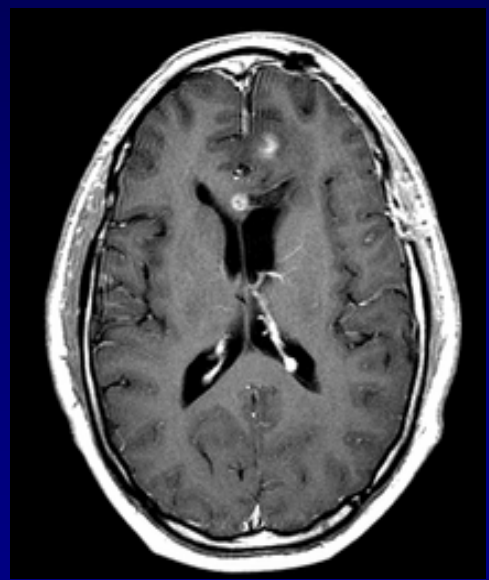


Axial Sagittal Coronal

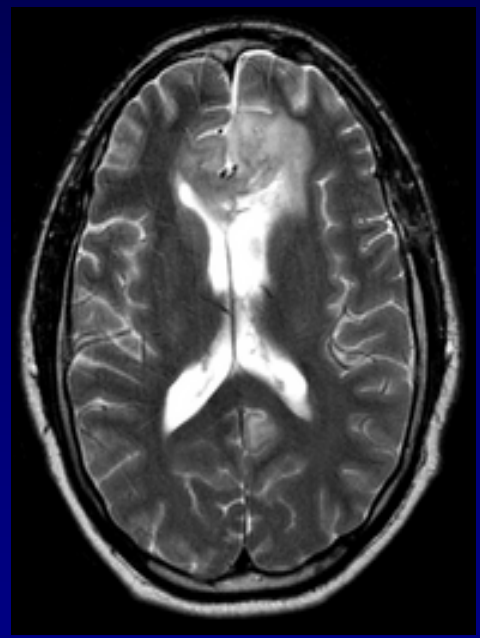
MRI – image types



T1



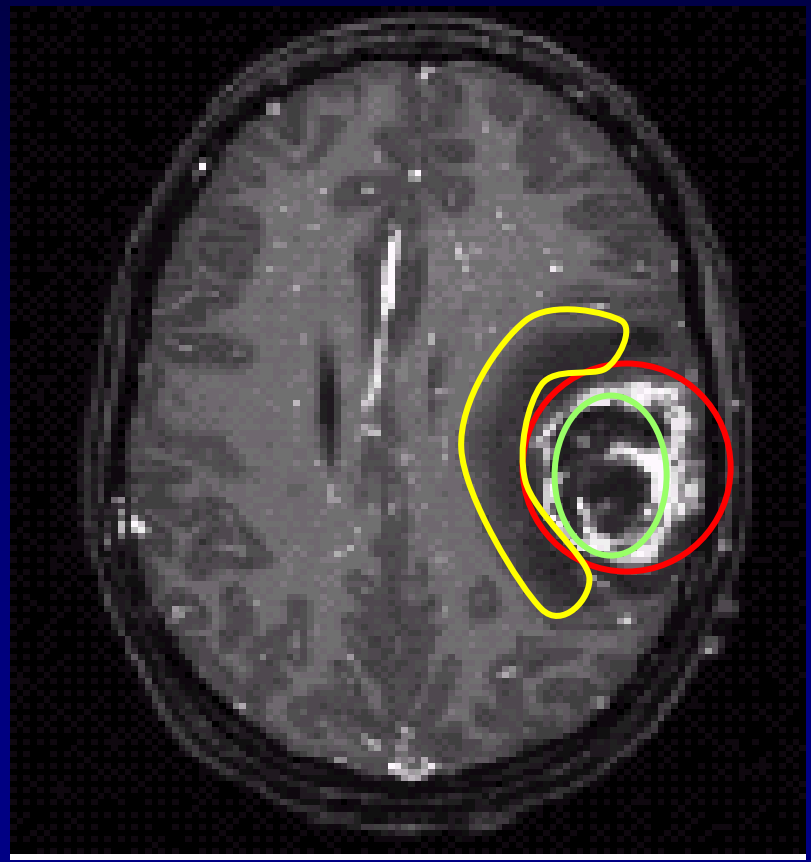
T1-contrast



T2

T1-Contrast scan (axial)

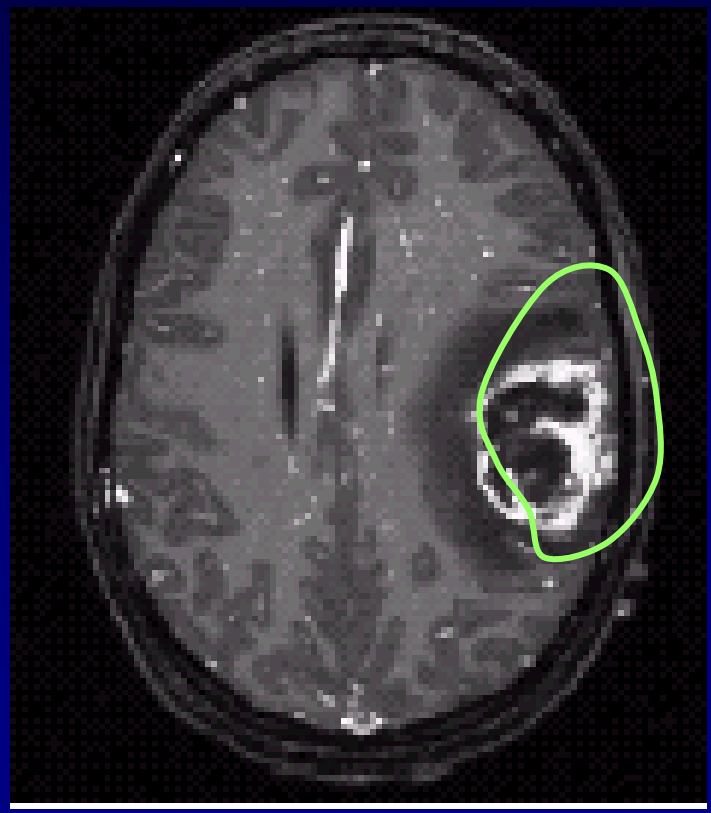
- Tumour is bright white structure
- Necrotic region is black structure
  - dead cells in center of tumour
- Edema may surround tumour
  - swelling of normal tissue



Better Treatment Region

Irradiate

- Tumour
- Occult cells
- Minimal number of normal cells - minimize loss of brain function
- Higher dose of radiation – smaller chance of recurrent cancer



Better Approach

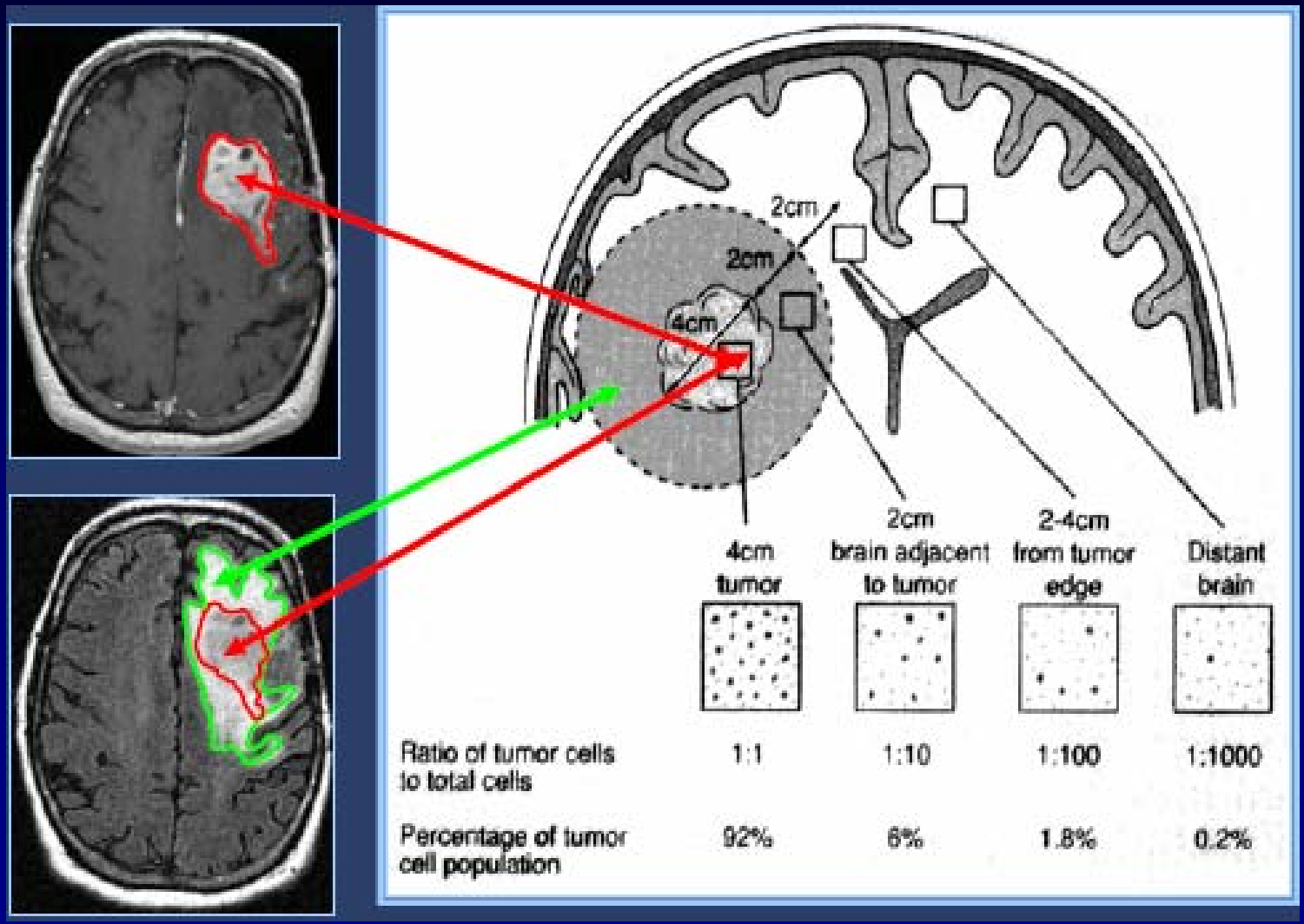
- *Locate brain tumours from MRI scan*
- Predict “(radiologically) occult” cancer cells surrounding tumour
  - predictor learned from earlier MRI data sets
- Treat tumour + predicted-occult region
- Meaningful as current techniques can zap arbitrary shapes!

RATIONALE

Underlying assumptions

- Occult cells ≡ future tumour growth
- Probability of growth of tumour T into adjacent voxel V is determined by
  - properties of T: growth rate, histology
  - properties of V: location, intensity, tissue type
- Voxel properties are known throughout brain
- Uniformity of brain tumour characteristics

Importance of Peri-tumoral Targeting

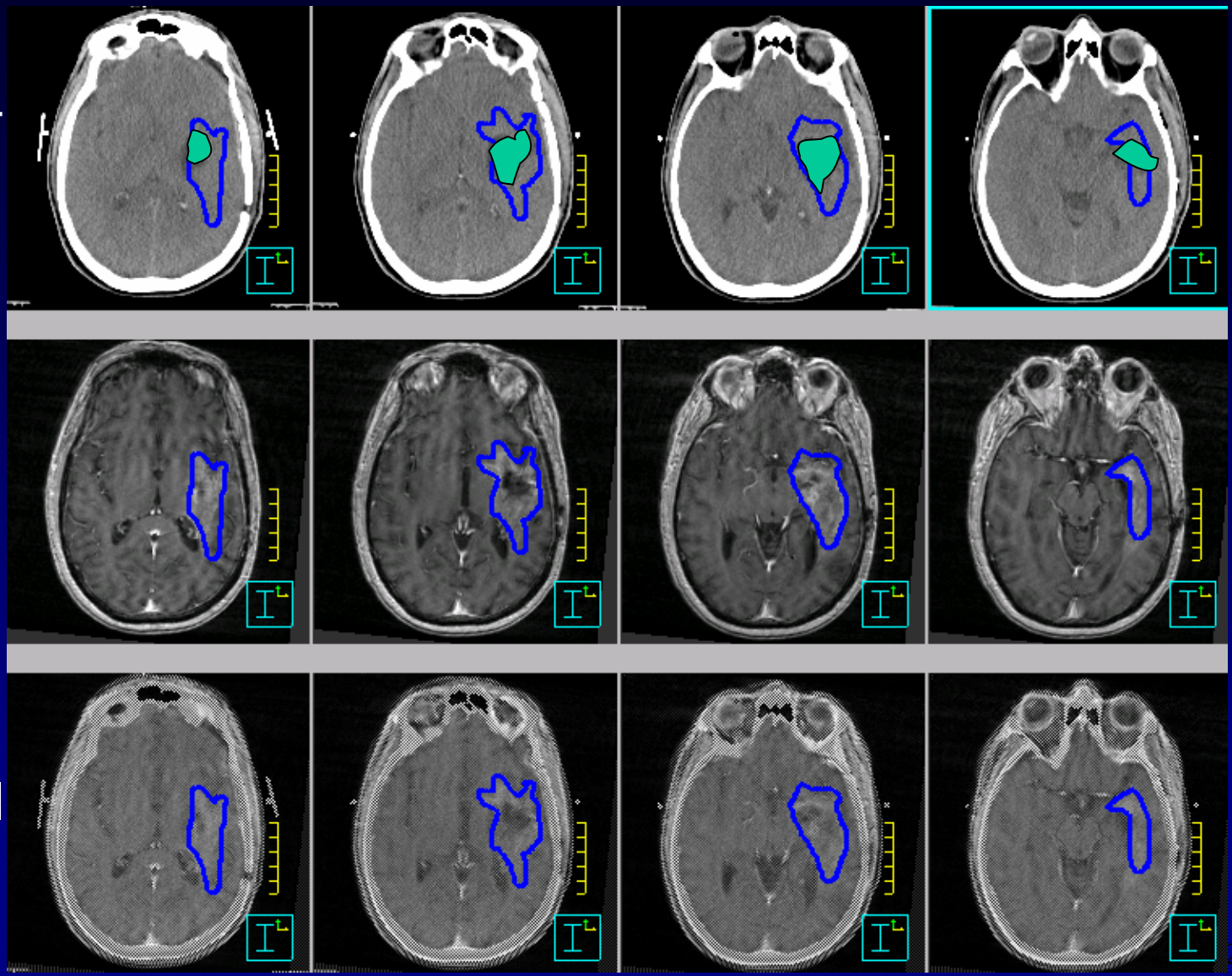


Tumor Definition: Traditional Methods

CT

MRI

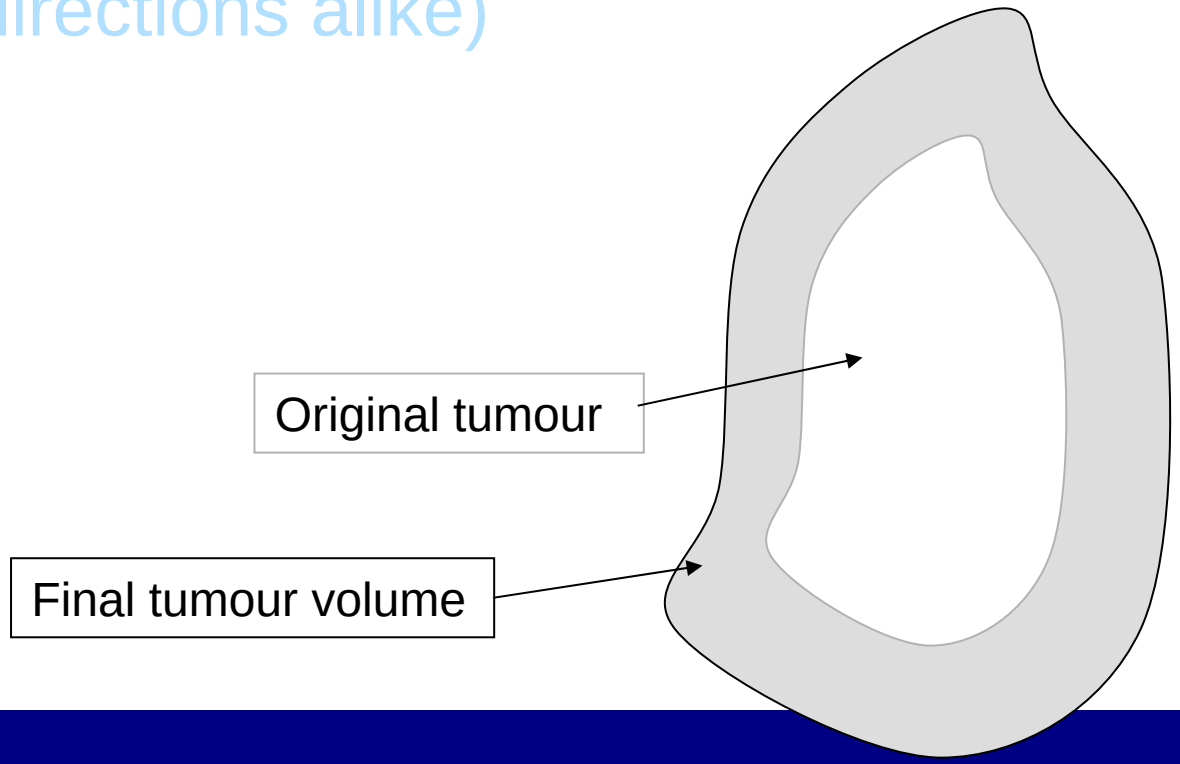
CT+MRI



~100 % local failure by 2 years; >90% within 2 cm of original XRT field margins

Tumour growth modeling

- Radial uniform growth
  (in all directions alike)



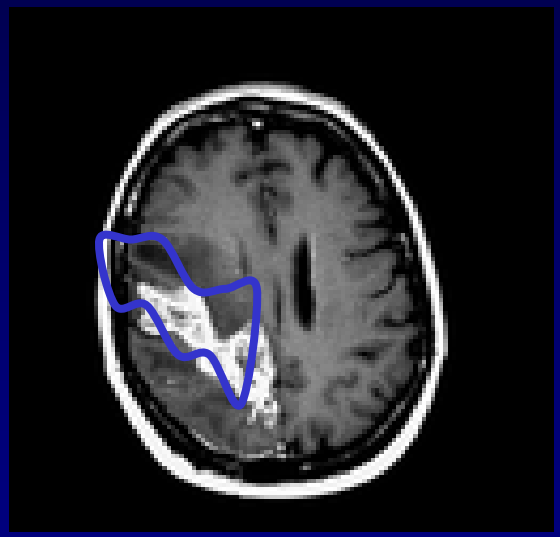
Features

- Patient attributes
  - Age
    - Correlation between age and glioma grade (more aggressive tumours occur in older patients; benign tumours in children)

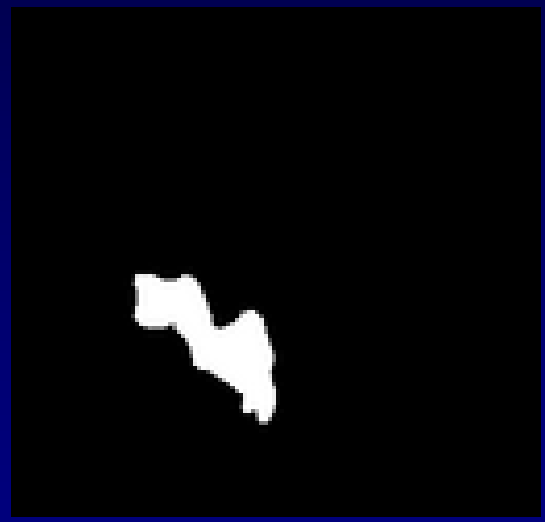
Features

- Tumour properties
  - Growth rate of tumour mass
  - Percentage of edema
  - Area-volume ratio
  - Volume increase between 2 scans

Tumour segmentation



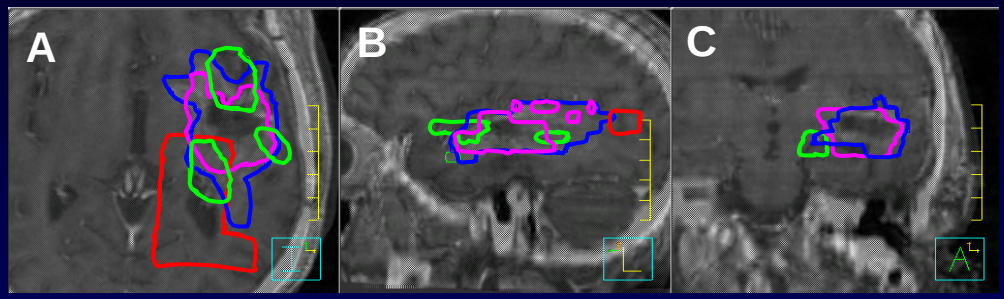
Slice from patient’s scan



Segmented tumour

Tumour contour drawn by human experts

Smart Targeting: Physiological MRI maps and Functional Imaging with PET



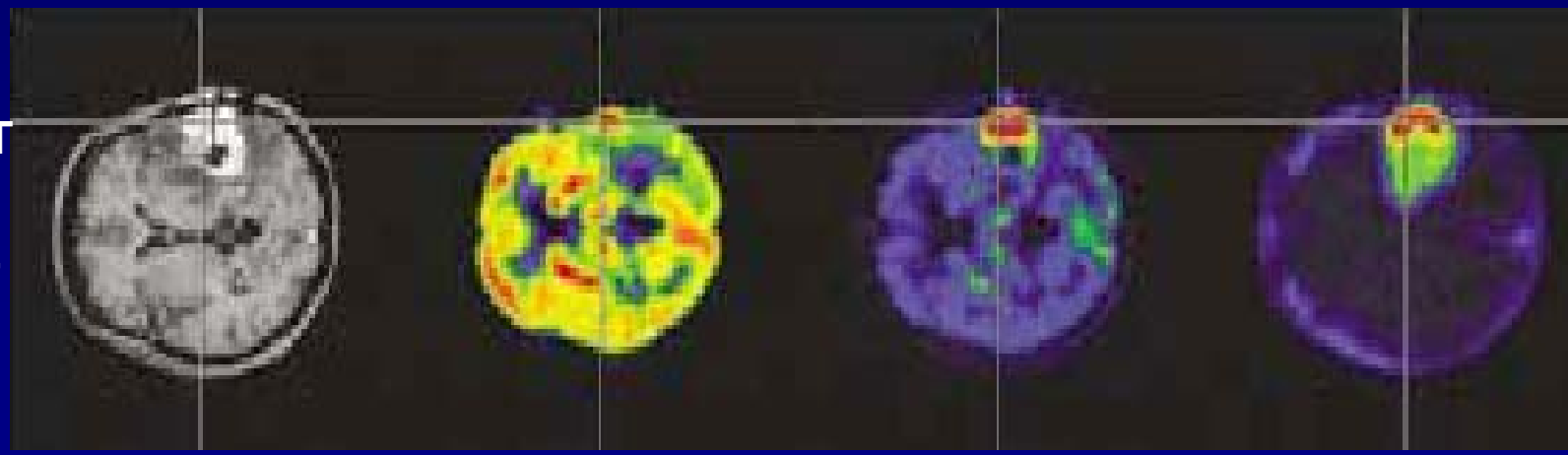
GTV=blue $CTV_{perfusion}$= green $CTV_{hypoxia}$= pink CTV_{CSI} = red

MRI

F-18 FDG PET

C-11 Met PET

F-18 FLT PET



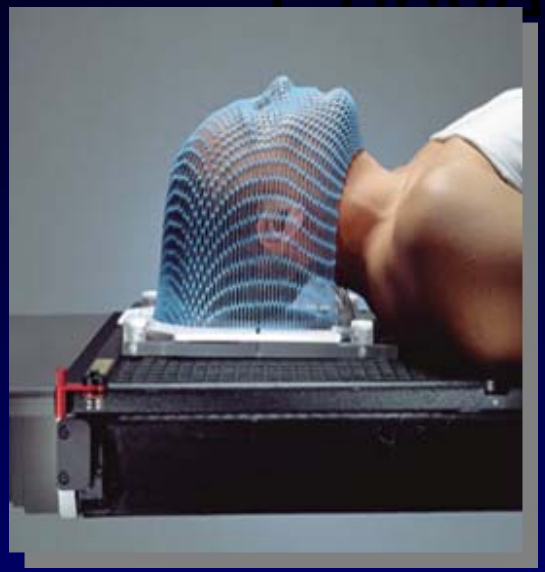
Jacobs, Technology in Ca Res & Treatment, July 2002

Structures of Interest Delineation

- Target and critical structure volumes may be defined by the physician, physicist and/or dosimetrist multi-group effort
  - IMRT communication
- Contouring accuracy is very important

(Inverse planning)

Conventional Radiotherapy



Standard immobilisation shell

CT planning scan

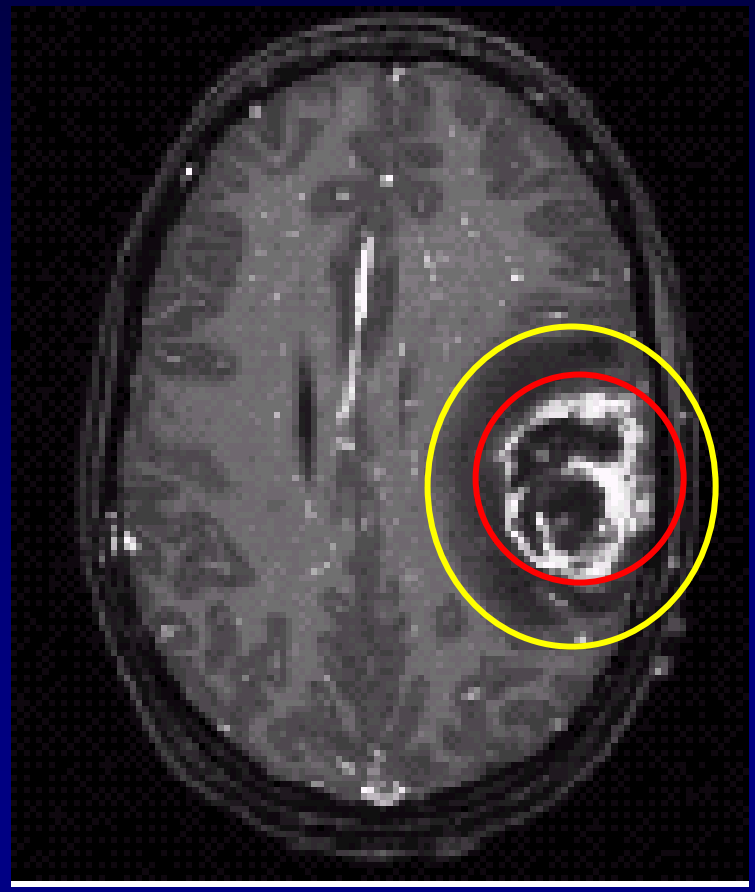
Fractionated treatment
(30 usually)

Current Treatment Region

Irradiate everything within 3 cm margin around tumour

... includes

- Occult cells
- Normal cells



Related work

- Modeling *macroscopic* glioma growth
  - 3D cellular automata (Kansal et al., 2000)
  - Differential motility in grey vs. white matter (Swanson et al., 2002)
  - White matter tract invasion (Clatz et al., 2004)
  - Supervised treatment planning (Zizzari, 2004)

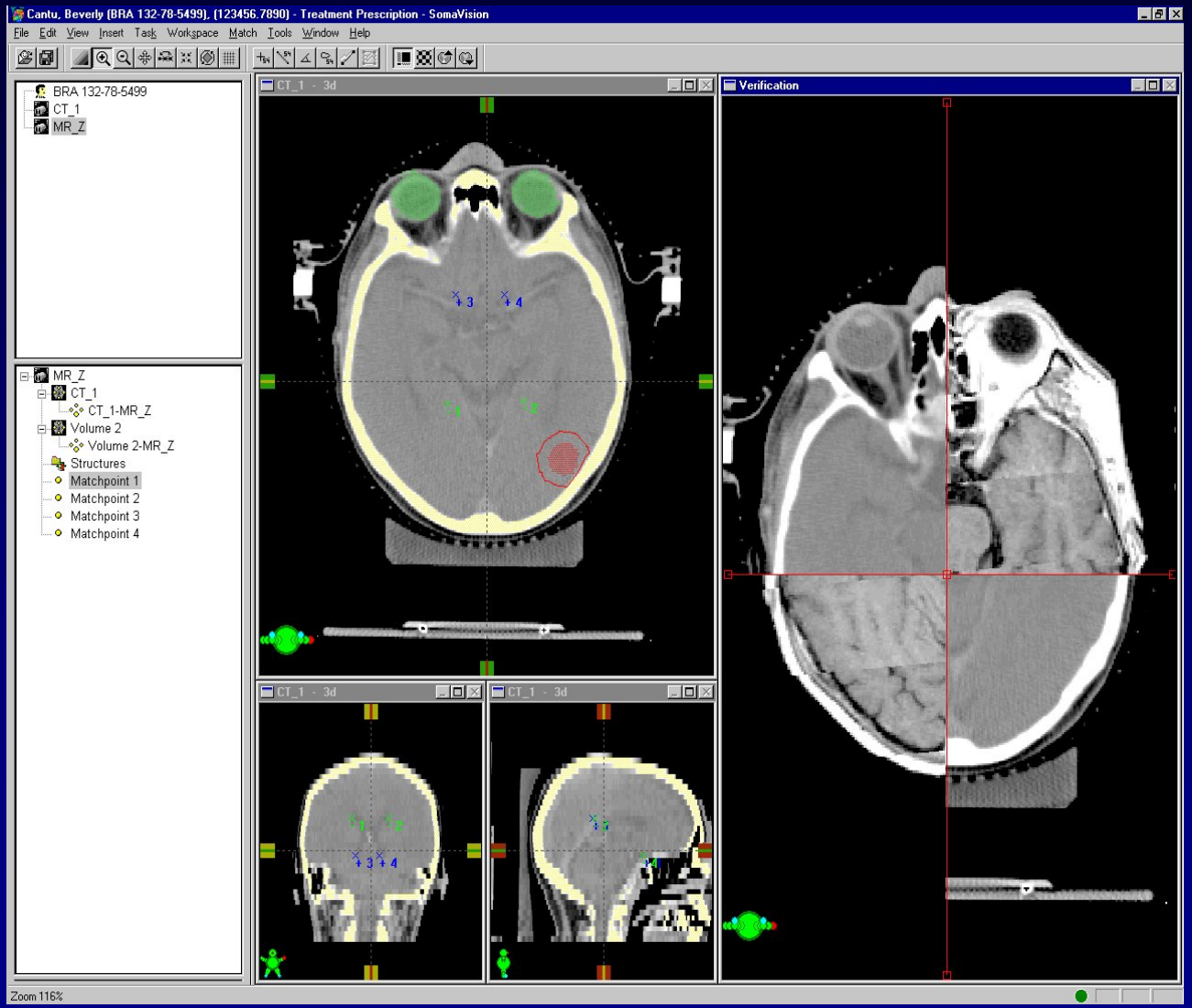
Related work

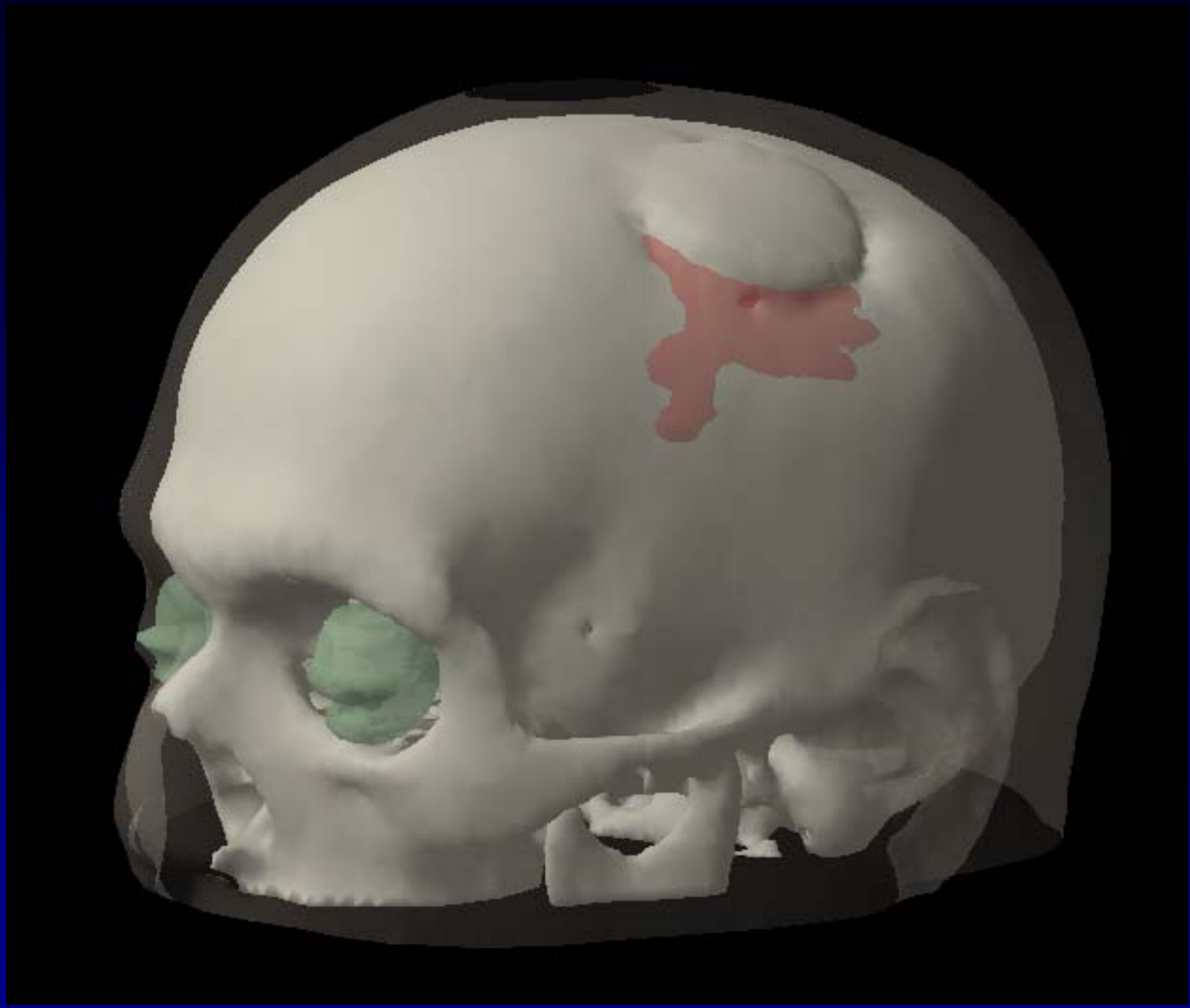
- White matter tract invasion – DTI*
- Uses anatomical atlas of white fibers
- Initiates simulation from a tumour at time 1
- Uses diffusion-reaction equation
- Evaluates results against tumour at time 2
  - Only one test patient (GBM)

*Diffusion Tensor Imaging

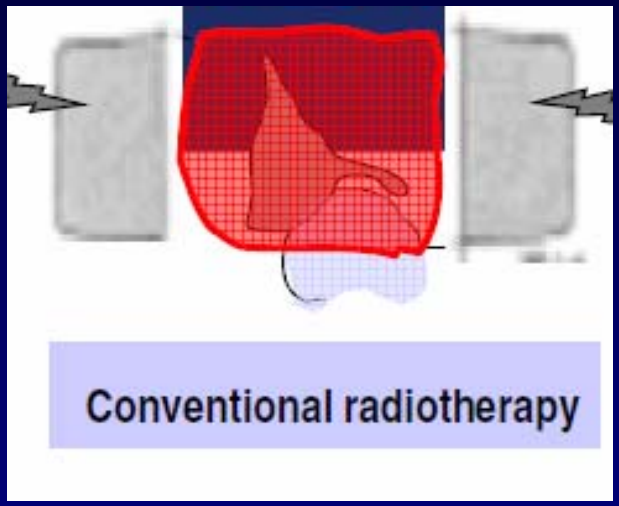
Clatz et al., 2004

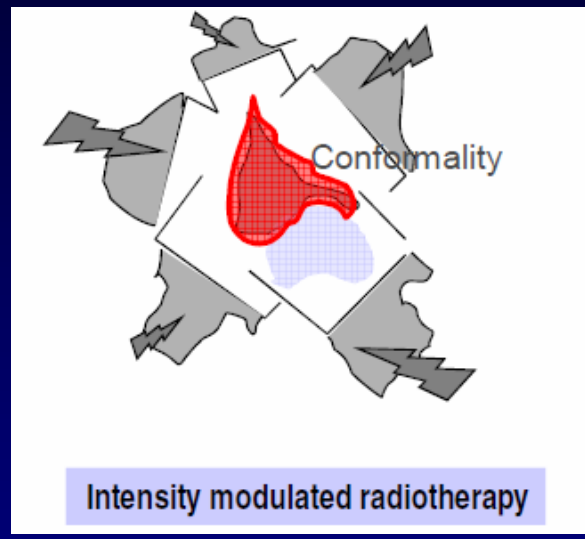
Contouring

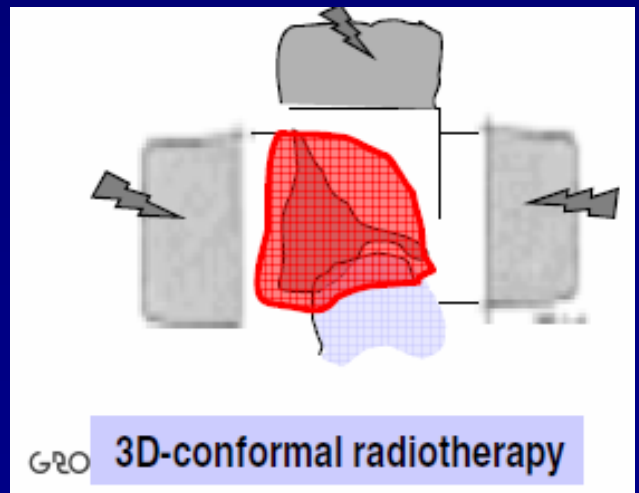

Cantu, Beverly (BRA 132-78-5499), (123456.7890) - Treatment Prescription - SomaVision
File Edit View Insert Task Workspace Match Tools Window Help
BRA 132-78-5499
CT_1
MR_Z
MR_Z
CT_1
CT_1-MR_Z
Volume 2
Volume 2-MR_Z
Structures
Matchpoint 1
Matchpoint 2
Matchpoint 3
Matchpoint 4
CT_1 - 3d
CT_1 - 3d
CT_1 - 3d
Verification
Zoom 116%



Radiotherapy techniques







CT/MR Acquisition/Simulation

- **CECT scan of the head acquired**
- **MR registered to planning CT (visual, surface matching, MI)**
  - T1 w/ contrast: excellent visualization of GBM
  - T2: edema (often involved by infiltrating gliomas)
  - T1 FLAIR: differentiate infiltrated brain vs. edema; delineation of nonenhancing lesions (grade 2 glioma)
- ~3 mm slice thickness maximum for accurate structure representation
- ~1 mm slice thickness: stereotactic, small lesions

Impact of different CT slice thickness on clinical target volume for 3D conformal radiation therapy. Prabhakar R, Ganesh T, Rath GK, Julka PK, Sridhar PS, Joshi RC, Thulkar S. Med Dosim. 2009 Spring;34(1):36-41.
For 3D conformal radiotherapy treatment planning (3DCRT), a CT slice thickness of 2.5 mm is optimum for tumor volume <25 cc, and 5 mm is optimum for tumor volume >25 cc.

Whether MRI alone can be used for treatment planning?

MRI-based treatment planning for brain lesions is feasible and gives equivalent dosimetric results compared to CT-based treatment planning.

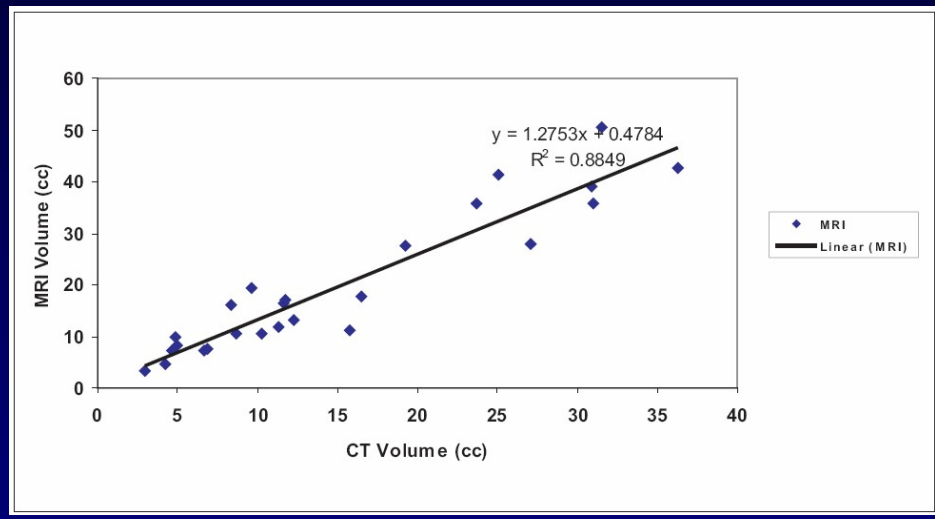
The maximum distortion in the MRI phantom study was less than 1 mm.

Feasibility of using MRI alone for 3D radiation treatment planning in brain tumors. Prabhakar R, Julka PK, Ganesh T, Munshi A, Joshi RC, Rath GK. Jpn J Clin Oncol. 2007 Jun;37(6):405-11.

MRI, an indispensible modality for brain tumours

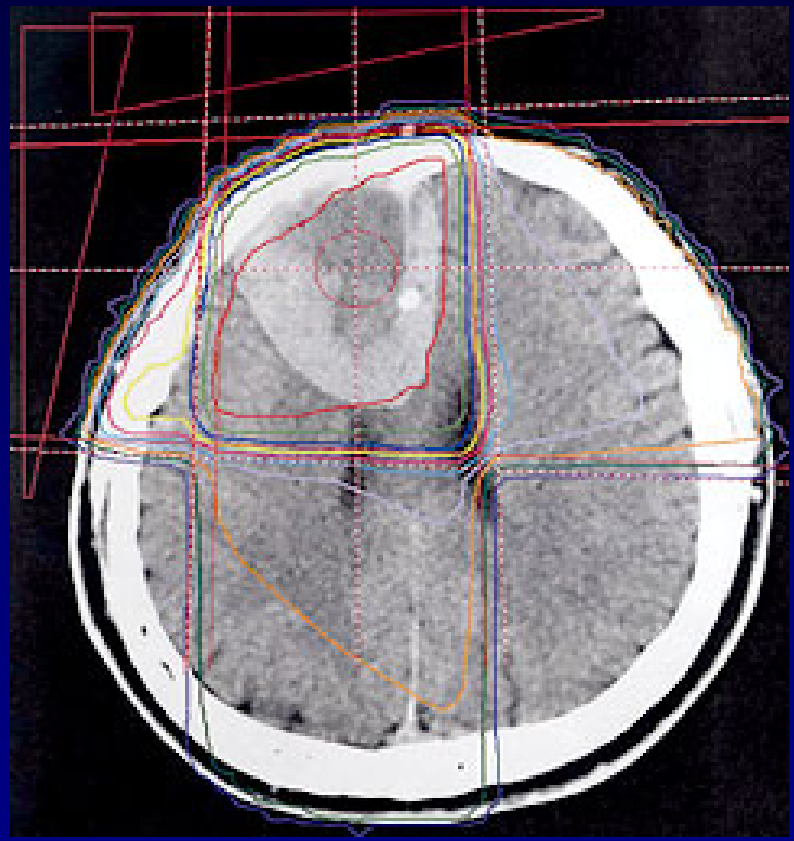
CT-based planning in brain tumor without the use of MRI will lead to under-dosage to the tumor.

In our study, except in the case of meningiomas in more than 44% of the patients, MRI showed more than 40% increase in the tumor volume.



Comparison of computed tomography and magnetic resonance based target volume in brain tumors. Prabhakar R, Haresh KP, Ganesh T, Joshi RC, Julka PK, Rath GK. J Cancer Res Ther. 2007 Apr-Jun;3(2):121-3.

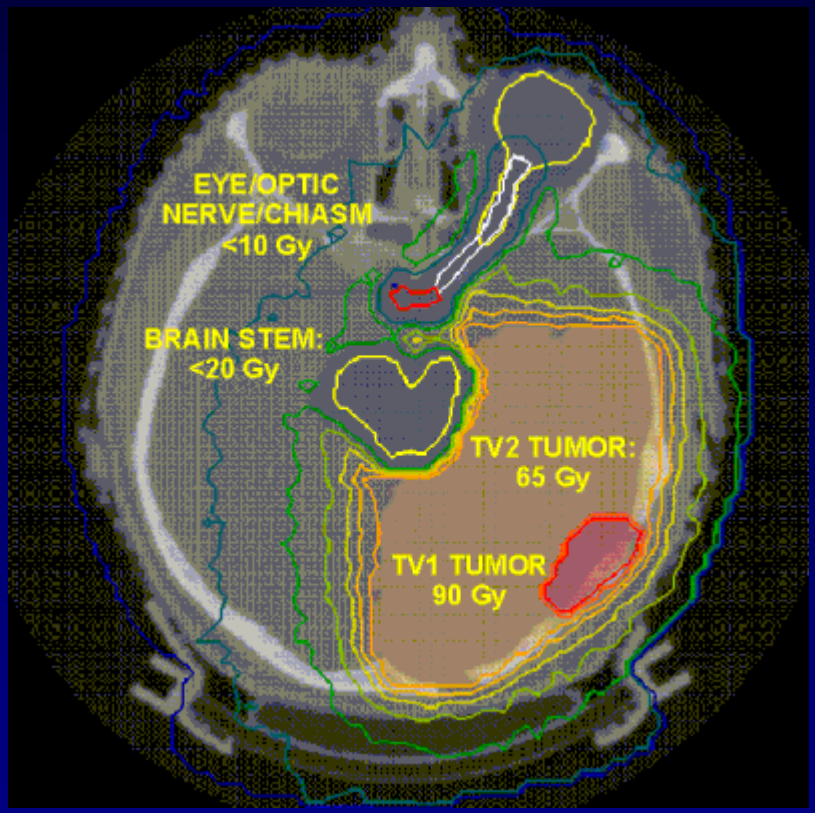
Conventional Radiotherapy

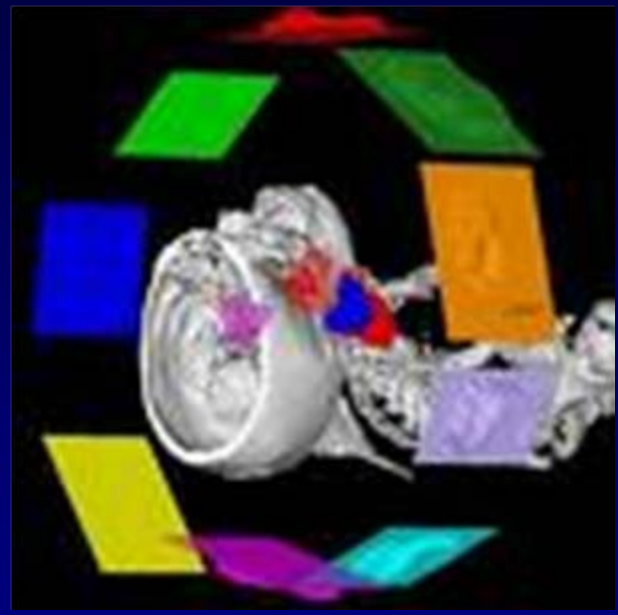


CNS Organs at Risk

- optic chiasm: 54 Gy (max threshold)
- optic nerves: 60 Gy
- optic globes: 50 Gy
- brainstem: 54 Gy
- temporal lobes: 25-30 Gy
- contralateral brain: 45 Gy or 25-30 Gy
- pituitary: 50 Gy
- spinal cord: 50 Gy
- inner ears: minimize
- area postrema (nausea): minimize
- other involved brain tissue: minimize

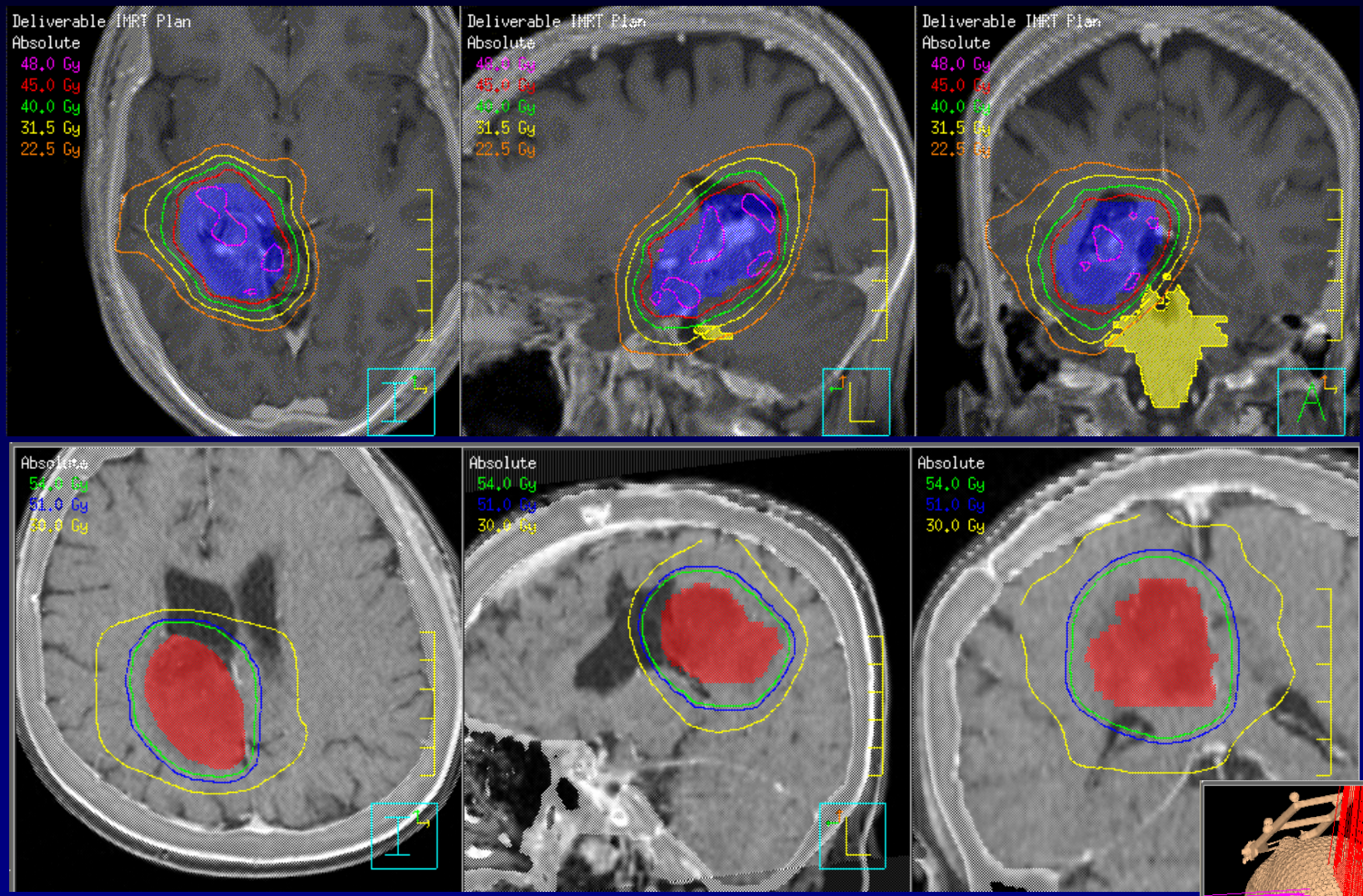
Intensity Modulated Radiotherapy (I.M.R.T.)





Multiple beams, non uniform dose across the beam

Typical RT Dose Distributions GBM



Why IMRT for the Gliomas?

•Improved conformality and avoidance of normal structures - multiple structures confined to cranial vault.

•Improved homogeneous dose delivery (irregularly shaped lesion and/or external contour) Allow for dose escalation - improved local control.

• IMRT in gliomas is not to reduce the margins.

Example: GBM
heterogeneous cell population
increase dose/fx to gross tumor volume

Advanced Techniques : SRS & SRT

- ‘delivery of a high dose of radiation in a **single fraction** to a small and precisely delineated intracranial lesion’ → **Stereotactic RadioSurgery (SRS)**

- ‘delivery of conventional fractionated dose over **multiple fractions** to a small and precisely delineated intracranial lesion’ → **Stereotactic RadioTherapy (SRT)**

Vision for the Future: Patient Specific Treatment Strategies

Selection of Therapeutic Approach

- **High resolution anatomic imaging**

  – provide information on tumor size and location to guide in the selection of the radiation beam

- **Genetic profiling**

  – indicate the molecular targets that are present in high concentration on the tumor

- **Molecular imaging**

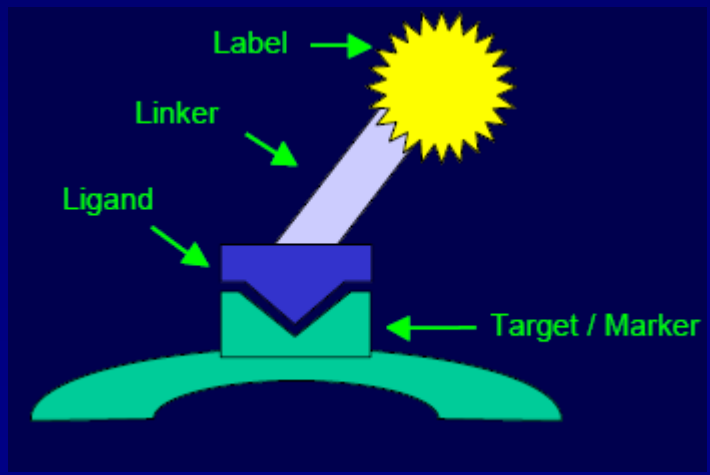
  – identify optimal therapeutic targets that are overexpressed and accessible on the tumor cells

Molecular Imaging

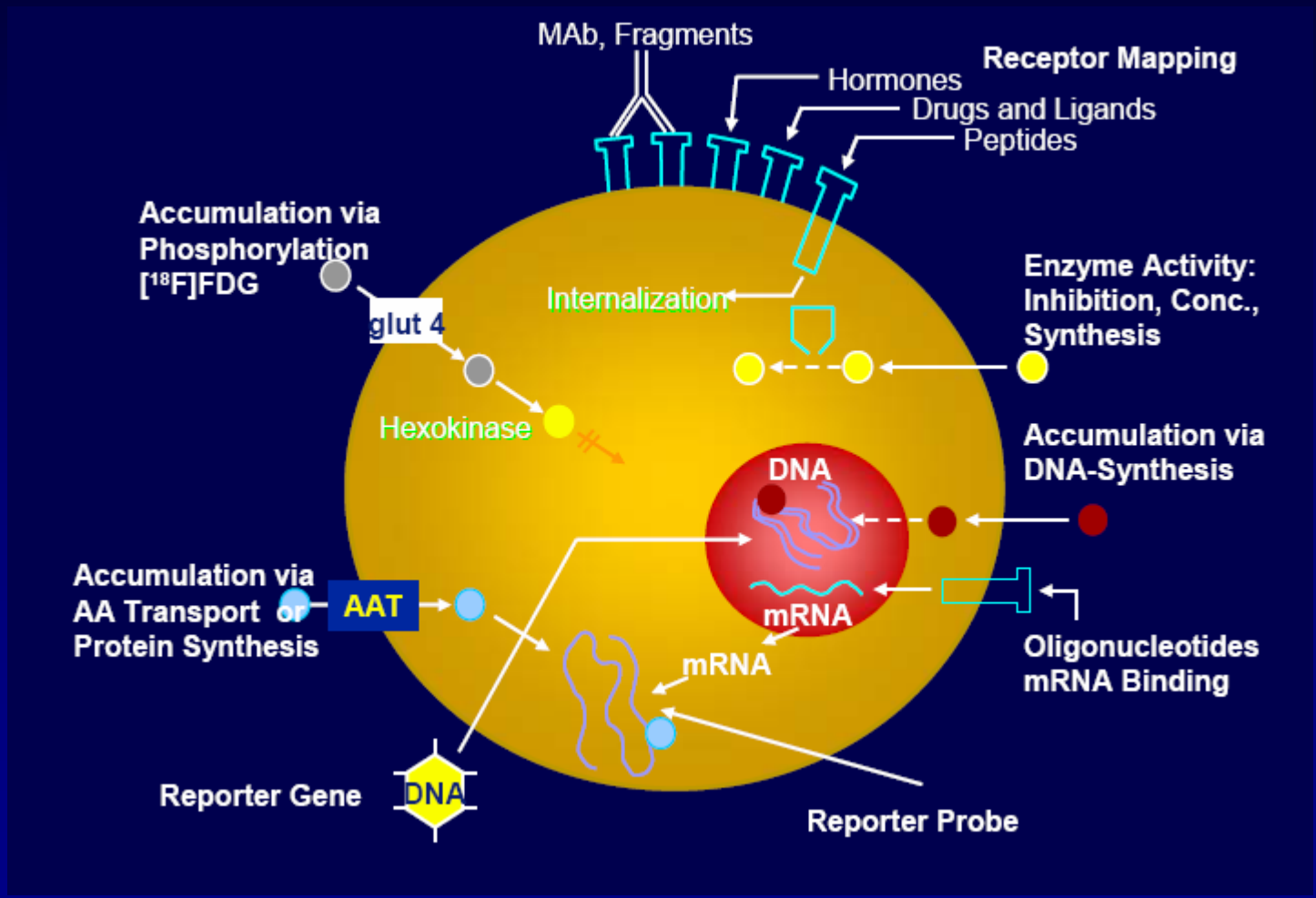
- Early detection
- Characterization of disease
- Biology
- Treatment evaluation

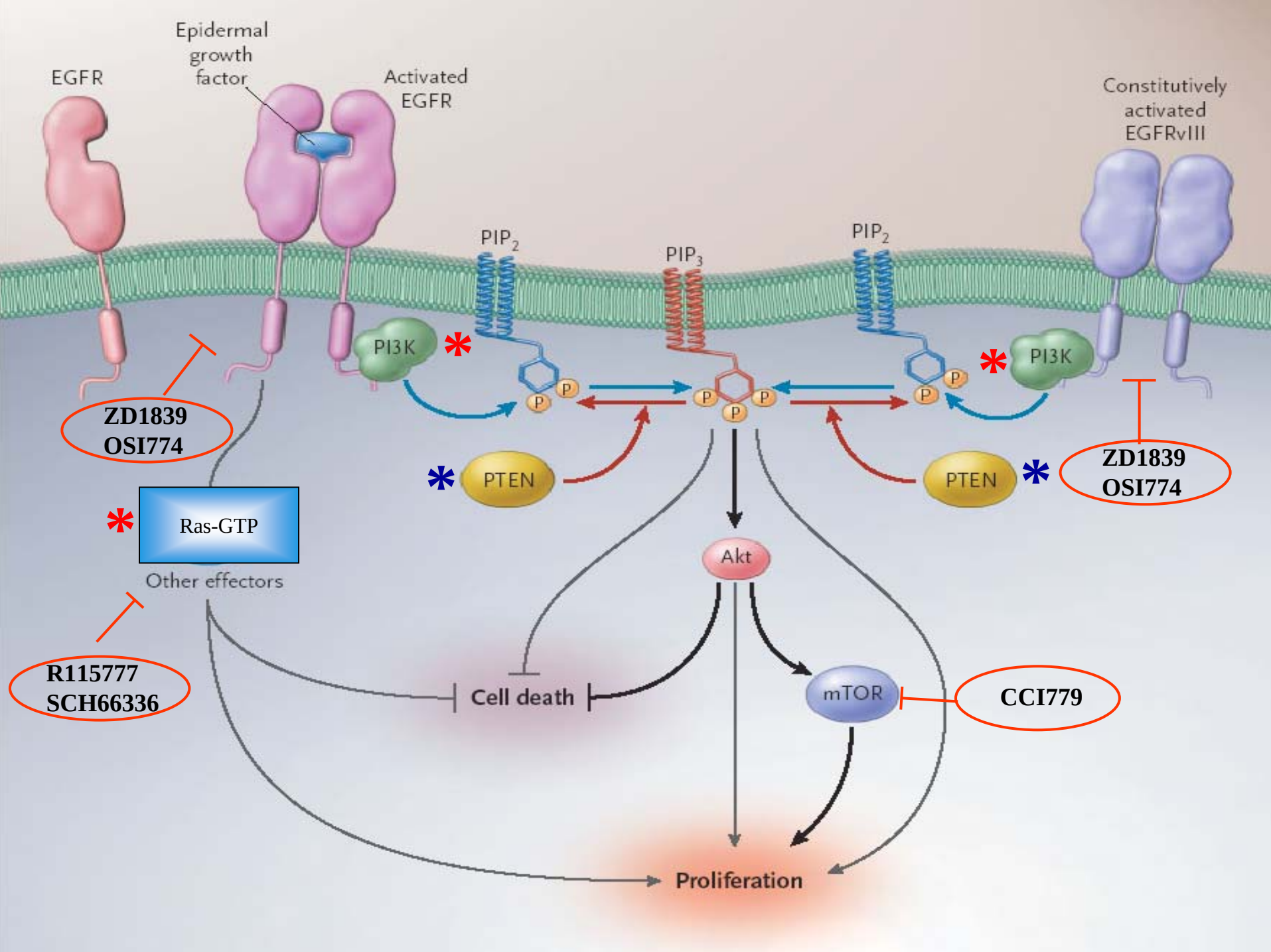
Molecular imaging

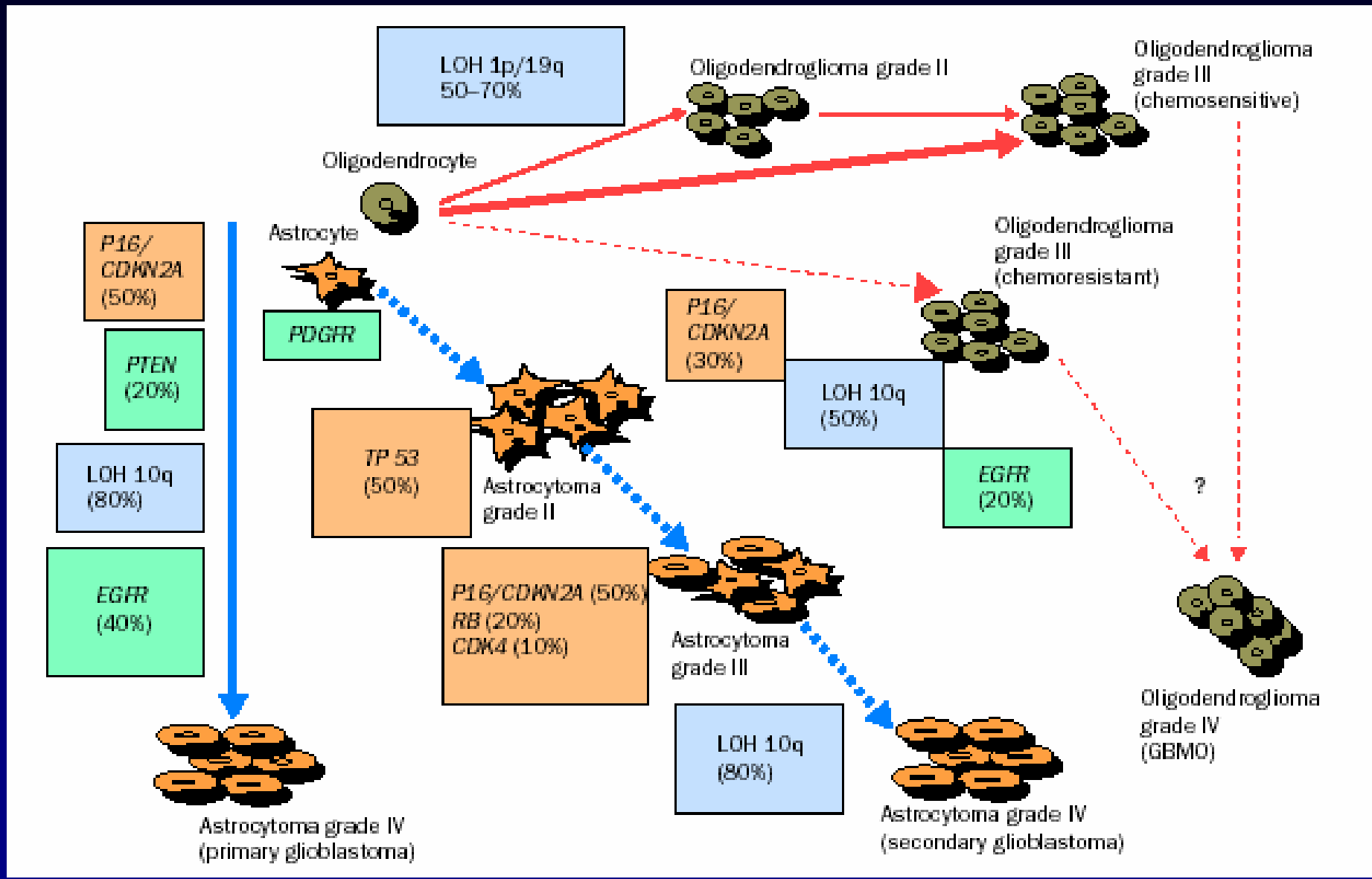
- Targeted contrast agents are key for molecular imaging
- Ligand that links the target
- Label which “makes the contrast
- Linker to connect label with ligand



Molecular Imaging Targets/Probes




EGFR
Epidermal growth factor
Activated EGFR
Constitutively activated EGFRvIII
PIP2
PIP3
PIP2
PI3K
PI3K
P
ZD1839
OSI774
PTEN
PTEN
ZD1839
OSI774
Ras-GTP
Other effectors
Akt
R115777
SCH66336
Cell death
mTOR
CCI779
Proliferation


LOH 1p/19q
50–70%
Oligodendroglioma grade II
Oligodendroglioma
grade III
(chemosensitive)
Oligodendrocyte
Astrocyte
P16/
CDKN2A
(50%)
PDGFR
PTEN
(20%)
LOH 10q
(80%)
EGFR
(40%)
Oligodendroglioma
grade III
(chemoresistant)
P16/
CDKN2A
(30%)
LOH 10q
(50%)
EGFR
(20%)
?
TP 53
(50%)
Astrocytoma
grade II
P16/CDKN2A (50%)
RB (20%)
CDK4 (10%)
Astrocytoma
grade III
LOH 10q
(80%)
Oligodendroglioma
grade IV
(GBMO)
Astrocytoma grade IV
(primary glioblastoma)
Astrocytoma grade IV
(secondary glioblastoma)

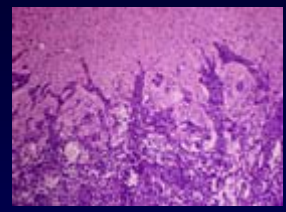
Future MR imaging

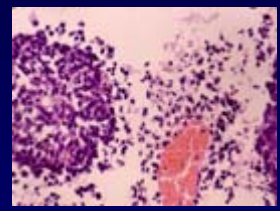
- Advances in MR Imaging
- Diffusion-weighted imaging
- Perfusion-weighted imaging
- Proton MR Spectroscopy

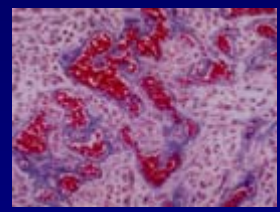
Anatomy → Physiology → Biology

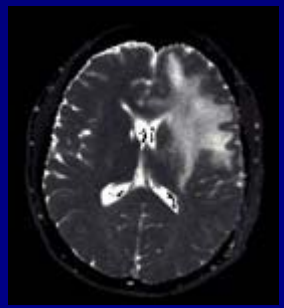
Key biologic hallmarks of GBM

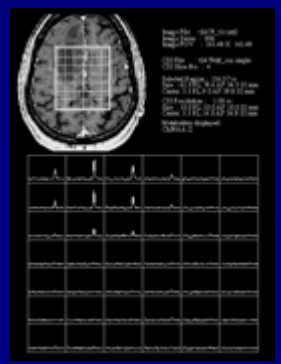
- Infiltration/invasion
- Hypoxia/Necrosis
- Angiogenesis

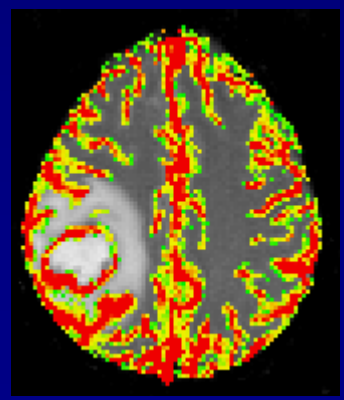




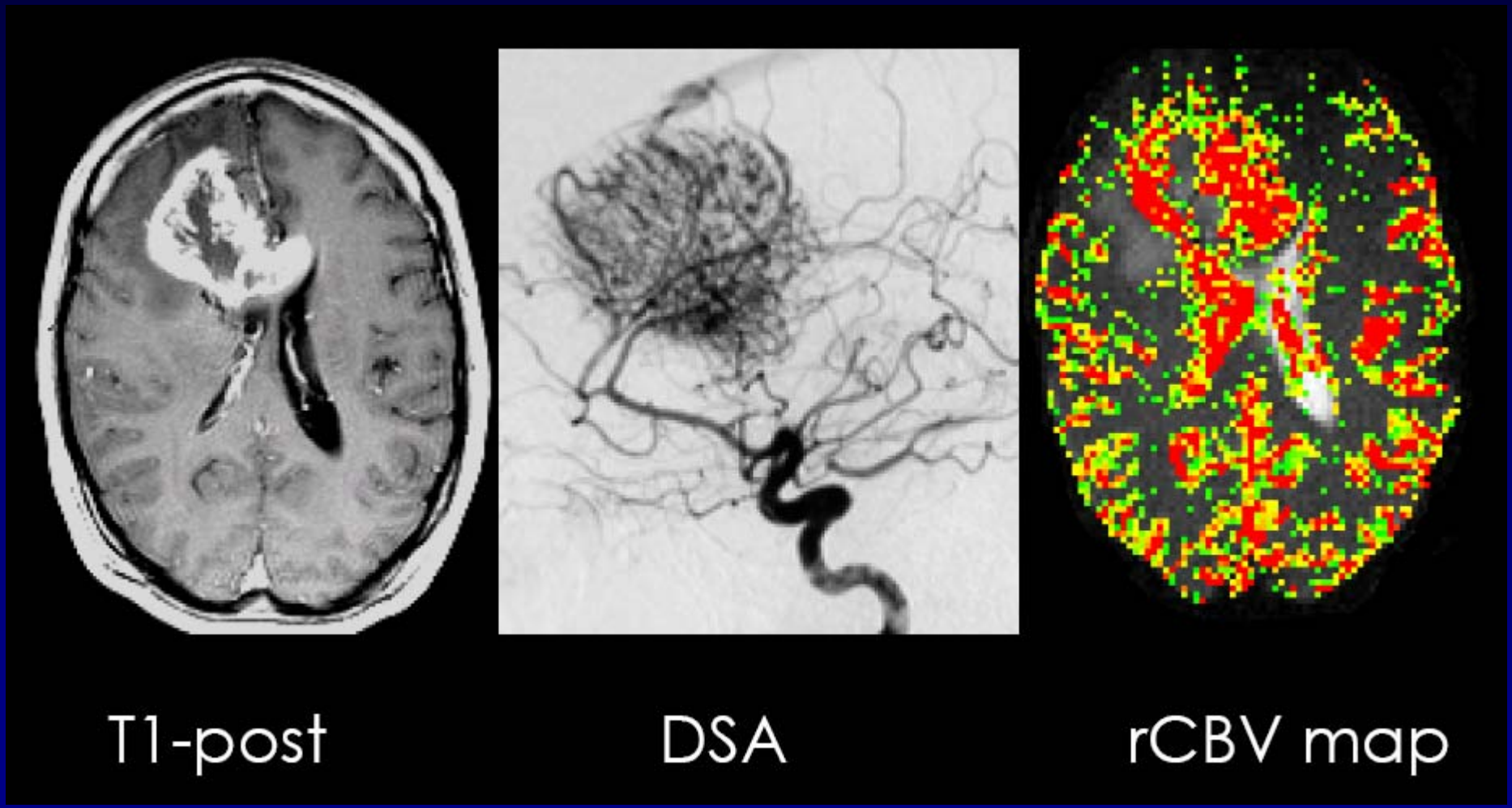








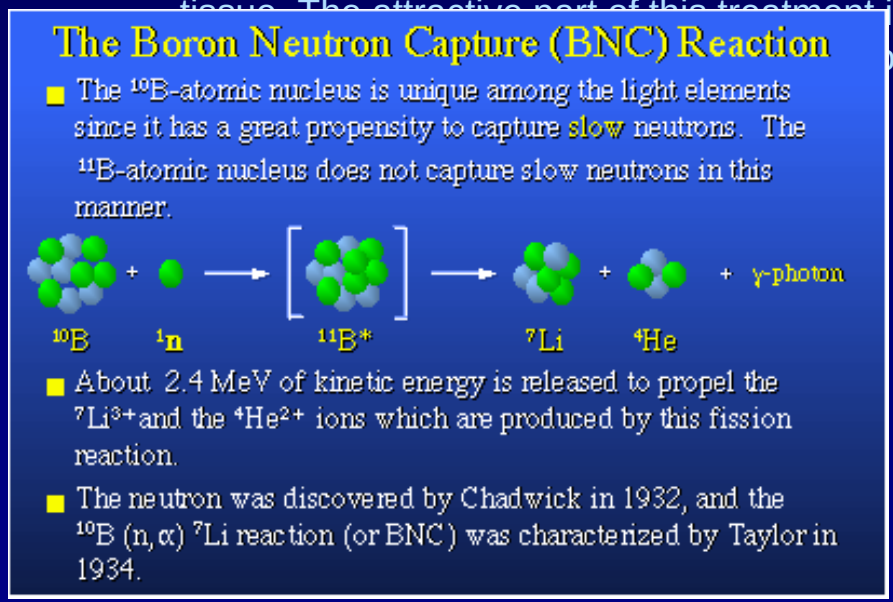
GBM

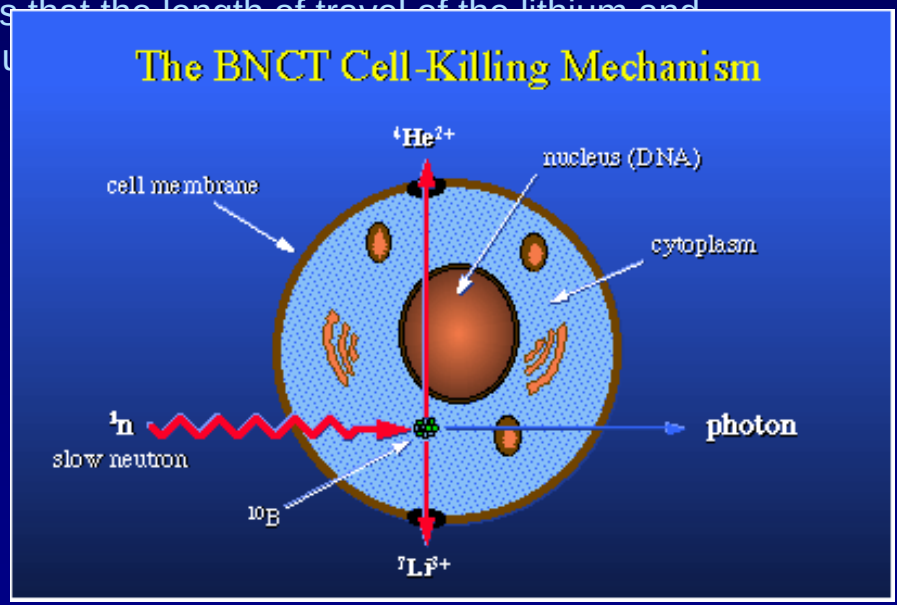


Thank you

Boron Neutron Capture Therapy

- studied as a treatment for glioblastoma multiforma
- The destruction of tissue would be localized to only the cancerous cells, since they are the only ones that contain boron-10. The BNC (boron neutron capture) would kill the targeted tumor cells and the body could heal itself, replacing the dead tumor tissue with normal





BNCT

- no controlled comparative studies that compare BNCT to conventional therapy
- To date, only followup studies with small numbers of patients have been performed
- One of these studies reports a relapse pattern after BNCT which is similar to that after conventional therapy
  - Median survival was 13 months, which is also similar to that after conventional radiotherapy
  - An advantage with BNCT is that treatment time is only about 3 days, compared to 6 weeks for conventional radiotherapy.
  - To date, no serious side effects have been reported after BNCT. However, it should be emphasized that given the limited experience to date, knowledge concerning side effects is insufficient.