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

61 mths. follow up

R- 1.9 (0.6-4.4)
C- 9.8 (6.4-14.0)

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

<table>
<thead>
<tr>
<th>Prognostic Factor (reference level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization</td>
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<tr>
<td>&lt; 40 years</td>
</tr>
<tr>
<td>≥ 40 years</td>
</tr>
<tr>
<td>Largest diameter of the tumor</td>
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<tr>
<td>&lt; 6 cm</td>
</tr>
<tr>
<td>≥ 6 cm</td>
</tr>
<tr>
<td>Tumor crossing midline</td>
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<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Histology type</td>
</tr>
<tr>
<td>Oligo/mixed</td>
</tr>
<tr>
<td>Astrocytoma</td>
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<tr>
<td>Neurologic deficit</td>
</tr>
<tr>
<td>Absent</td>
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<tr>
<td>Present</td>
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</tbody>
</table>

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

- Cortex
- Corpus Callosum
- White matter
- Grey matter
- Ventricles (contain CSF)
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!
Underlying assumptions

- Occult cells $\equiv$ 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\textsubscript{perfusion}= green  CTV\textsubscript{hypoxia}= pink  CTV\textsubscript{CSI}= red

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
Radiotherapy techniques

Conventional radiotherapy

3D-conformal radiotherapy

Intensity modulated radiotherapy

Conformality
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


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.

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.

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

Accumulation via Phosphorylation
["^18F"]FDG

Internalization

Hexokinase

Accumulation via AA Transport
Protein Synthesis

AAT

Reporter Gene

DNA

MAB, Fragments

Receptor Mapping

Hormones

Drugs and Ligands

Peptides

Enzyme Activity:
Inhibition, Conc.,
Synthesis

Accumulation via
DNA-Synthesis

Oligonucleotides
mRNA Binding

Reporter Probe

mRNA
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

T1-post  DSA  rCBV map
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 tissue. The attractive part of this treatment is that the length of travel of the lithium and helium ions produced from BNC is only about one cell thick.

The Boron Neutron Capture (BNC) Reaction

- The $^{10}$B-atomic nucleus is unique among the light elements since it has a great propensity to capture slow neutrons. The $^{11}$B-atomic nucleus does not capture slow neutrons in this manner.

\[
\begin{align*}
^{10}\text{B} + ^{1}\text{n} & \rightarrow [^{11}\text{B}^*] \\
& \rightarrow ^{7}\text{Li} + ^{4}\text{He} + \gamma\text{photon}
\end{align*}
\]

- About 2.4 MeV of kinetic energy is released to propel the $^{7}\text{Li}^2+$ and the $^{4}\text{He}^2+$ ions which are produced by this fission reaction.

- The neutron was discovered by Chadwick in 1932, and the $^{10}\text{B} (n, \alpha) ^{7}\text{Li}$ reaction (or BNC) was characterized by Taylor in 1934.

The BNCT Cell-Killing Mechanism

- The cell membrane
- The nucleus (DNA)
- The cytoplasm
- The cytoplasm contains the slow neutron
- The $^{10}\text{B}$ and $^{7}\text{Li}$ ions
- The emitted photon
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.